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L1      STRUCTURE UPLOADED

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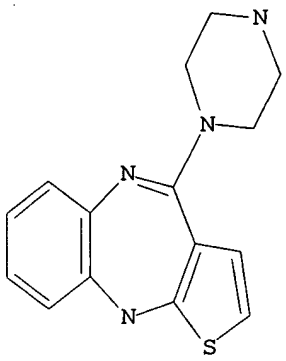


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SAMPLE SEARCH INITIATED 10:45:57 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      5 TO ITERATE
100.0% PROCESSED       5 ITERATIONS                                 5 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:             5 TO      234
PROJECTED ANSWERS:                5 TO      234

L2            5 SEA SSS SAM L1

=> s l1 ful

FULL SEARCH INITIATED 10:46:05 FILE 'REGISTRY'
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100.0% PROCESSED     109 ITERATIONS                               104 ANSWERS
SEARCH TIME: 00.00.01

L3          104 SEA SSS FUL L1

=> file caplus

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                                                 ENTRY    SESSION
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FILE COVERS 1967 - 11 Jan 1999 VOL 130 ISS 3
FILE LAST UPDATED: 11 Jan 1999 (19990111/ED)

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=> s l3

L4 182 L3

=> s l4 and (preparar? or preparation or produc? or synthesis)

20 PREPARAR?
963829 PREPARATION
2231765 PRODUC?
746440 SYNTHESIS
L5 35 L4 AND (PREPARAR? OR PREPARATION OR PRODUC? OR SYNTHESIS)

=> d l5 1- ibib abs hitstr

YOU HAVE REQUESTED DATA FROM 35 ANSWERS - CONTINUE? Y/(N):y

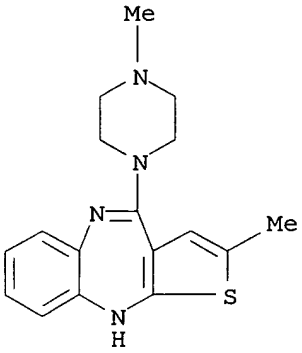
L5 ANSWER 1 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:622583 CAPLUS
DOCUMENT NUMBER: 129:326007
TITLE: Atypical antipsychotic drugs selectively increase neurotensin efflux in dopamine terminal regions
AUTHOR(S): Radke, James M.; Owens, Michael J.; Ritchie, James C.; Nemeroff, Charles B.
CORPORATE SOURCE: Departments of Psychiatry and Behavioral Sciences and tPathology, Emory University School of Medicine, Atlanta, GA, 30322, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1998), 95(19), 11462-11464
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Typical antipsychotic drugs, such as haloperidol and chlorpromazine, increase **synthesis** of the neuropeptide neurotensin (NT) in both the striatum and the nucleus accumbens, whereas atypical antipsychotic drugs, such as clozapine and olanzapine, do so only in the nucleus accumbens. By using in vivo microdialysis, we now report that acute administration of haloperidol, clozapine, or olanzapine failed to alter the release of NT in either the striatum or nucleus accumbens. In contrast, chronic administration of haloperidol for 21 days increased NT release in both the striatum and nucleus accumbens, whereas treatment for 21 days with the atypical antipsychotic drugs, clozapine or olanzapine, increased NT release selectively in the nucleus accumbens. These findings suggest that (i) increased NT mRNA expression and NT tissue concns. are assocd. with increases in the extracellular fluid concns. of the peptide and (ii) atypical antipsychotic drugs may exert their therapeutic effects and **produce** fewer side effects by virtue of their selectivity in limbic compared with striatal, target neurons.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(atypical antipsychotic drugs selectively increase neurotensin efflux in dopamine terminal regions)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 2 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:387563 CAPLUS

DOCUMENT NUMBER: 129:117385

TITLE: A comparison of the oxidation of clozapine and olanzapine to reactive metabolites and the toxicity of these metabolites to human leukocytes

AUTHOR(S): Gardner, Iain; Zahid, Nasir; MacCrimmon, Duncan; Uetrecht, Jack P.

CORPORATE SOURCE: Faculties of Pharmacy and Medicine, Unversity of Toronto, ON, Can.

SOURCE: Mol. Pharmacol. (1998), 53(6), 991-998

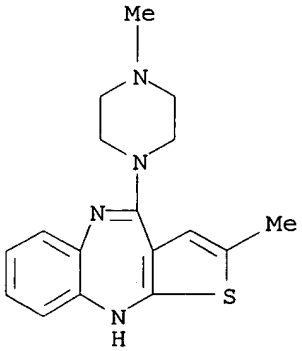
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Olanzapine is oxidized to a reactive intermediate by HOCl, the major oxidant **produced** by activated neutrophils. A mass spectrum obtained using a flow system in which the reactants were fed into a mixing chamber and the **products** flowed directly into the mass spectrometer revealed a reactive intermediate at m/z 311. This is 2 mass units less than the protonated mol. ion of parent olanzapine; thus the reactive intermediate may be a nitrenium ion. The reactive intermediate could be trapped with glutathione or N-acetylcysteine to **produce** two conjugates. The data are analogous to previous results on structurally related atypical antipsychotic agent clozapine. The clozapine and olanzapine reactive metabolites showed differences in their ability to cause toxicity to human neutrophils. Toxicity to neutrophils was obsd. only at high concns. of clozapine (>50 .mu.M) when HOCl was used to generate the reactive metabolite. A concn.-dependent toxicity was obsd. when neutrophils were incubated with clozapine (0-20 .mu.M) and H2O2 to generate the clozapine reactive metabolite. No toxicity was obsd. with clozapine alone at concns. >50 .mu.M. Similar results were obsd. in monocytes and HL-60 cells. Olanzapine reactive metabolite had only slight toxicity at the highest concns. tested (20 .mu.M), even when the reactive metabolite was generated using H2O2. Neutrophils from 2 patients with a history of clozapine-induced agranulocytosis seemed to be more sensitive to the toxic effects of the clozapine reactive metabolite.

IT **132539-06-1**, Olanzapine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(clozapine and olanzapine oxidative metabolites toxicity to human leukocytes)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 3 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:263237 CAPLUS

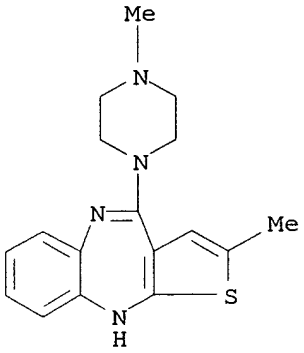
DOCUMENT NUMBER: 128:312930
TITLE: Olanzapine for treating insomnia
INVENTOR(S): Tran, Pierre Van
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5744470 | A | 19980428 | US 97-799052 | 19970210 |

AB The invention provides a method for treating insomnia comprising administering an effective amt. of olanzapine to an elderly patient who has been previously treated with a hypnotic agent. 2-Methyl-10H-thieno[2,3-b][1,5]benzodiazepin-4-amine.cntdot.HCl was treated with N-methylpiperazine to obtain olanzapine, which was suspended in anhyd. EtOAc while heating and the **product** was isolated using vacuum filtration. The **product** was identified as Form II using x-ray powder anal. A tablet was formulated contg. 1.18 % olanzapine.

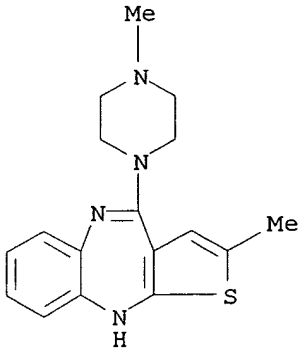
IT **132539-06-1P**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(olanzapine for treating insomnia)

RN 132539-06-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 4 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:235094 CAPLUS
DOCUMENT NUMBER: 128:303969
TITLE: Reversal of isolation rearing-induced deficits in prepulse inhibition by Seroquel and olanzapine
AUTHOR(S): Bakshi, Vaishali P.; Swerdlow, Neal R.; Braff,

David L.; Geyer, Mark A.
CORPORATE SOURCE: Department of Neurosciences, University of California at San Diego, La Jolla, CA, 92093-0804, USA
SOURCE: Biol. Psychiatry (1998), 43(6), 436-445
CODEN: BIPCBF; ISSN: 0006-3223
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Prepulse inhibition (PPI) of startle provides an operational measure of sensorimotor gating in which a weak stimulus presented prior to a startling stimulus reduces the startle response. PPI deficits obsd. in schizophrenia patients can be modeled in rats by individual housing from weaning until adulthood. Deficits in PPI **produced** by isolation rearing can be reversed by antipsychotics. We evaluated the ability of Seroquel and olanzapine to reverse the isolation-induced disruption of PPI. Rats housed for 8 wk singly or in groups of 3 were tested every 2 wk after either Seroquel (0, 5.0 mg/kg) or olanzapine (0, 2.5, 5.0 mg/kg). Startle was elicited by 120-dB pulses presented either with or without prepulses (3, 6, or 12 dB above a 65-dB background). Isolation rearing repeatedly disrupted PPI and sometimes increased startle reactivity. Seroquel reversed these deficits without affecting PPI in socially reared controls. Olanzapine (2.5 mg/kg) reversed the isolation rearing-induced PPI deficit and tended to increase basal PPI levels. Both antipsychotics antagonized the isolation rearing-induced increase in startle reactivity. Isolation rearing **produces** deficits in sensorimotor gating in rats that are reversible by atypical antipsychotics, and may therefore aid in identifying new treatments for schizophrenia.
IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(reversal of isolation rearing-induced deficits in prepulse inhibition by Seroquel and olanzapine)
RN 132539-06-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)

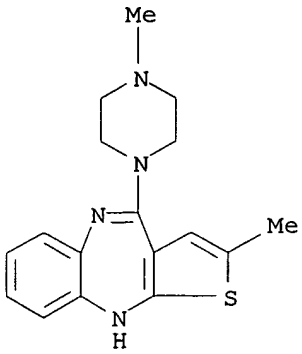


L5 ANSWER 5 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:168555 CAPLUS
DOCUMENT NUMBER: 128:290115
TITLE: Comparative characterization of the discriminative stimulus properties of clozapine and other antipsychotics in rats
AUTHOR(S): Goudie, Andrew; Taylor, Anita
CORPORATE SOURCE: Psychology Department, Liverpool University, Liverpool, L69 7ZA, UK
SOURCE: Psychopharmacology (Berlin) (1998), 135(4), 392-400
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The discriminative stimulus properties of the prototypical atypical neuroleptic clozapine (5 mg/kg, i.p.) were characterized in rats using a fixed ratio assay. Clozapine induced full dose-related generalization in the absence of response suppression. Amphetamine and pentylenetetrazol failed to generalize at doses known to be discriminable, showing a degree of specificity for the clozapine cue. The typical neuroleptics haloperidol and loxapine induced minimal (20%) generalization at doses with marked behavioral effects; thus clozapine discrimination dissocs. clozapine from typical neuroleptics. Atypical neuroleptics which are not clozapine congeners **produced** weak partial generalization when tested up to the highest doses that could be studied. The maximal levels of generalization induced by these agents were: amisulpiride 28%, risperidone 40% and sertindole 50%. Clozapine congeners typically caused more generalization, the novel pyridobenzoxapine JL13 inducing 70% maximal generalization. Most generalization (83%) was seen with the clozapine congener seroquel, although in contrast to clozapine, it only generalized at doses with marked effects on responding, so that no drug mimicked clozapine fully. Surprisingly, the clozapine congener olanzapine only induced a maximal level of 38% generalization. This apparently anomalous finding is attributed to an inability to test high doses of the drug due to its rate-suppressant actions. The clozapine cue can be used to rank atypical neuroleptics in terms of their similarity to clozapine in vivo. The clozapine cue is probably a compd. cue, since only agents showing "polyvalent" receptor pharmacol. induced substantial generalization.

IT **132539-06-1**, Olanzapine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative characterization of the discriminative stimulus properties of clozapine and other antipsychotics in rats)

RN 132539-06-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 6 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:98347 CAPLUS
DOCUMENT NUMBER: 128:176168
TITLE: Pharmaceutical compositions containing a 5-HT2C antagonist and a D2 antagonist for treatment of CNS disorders, including schizophrenia, and compound **preparation**
INVENTOR(S): Blackburn, Thomas Paul
PATENT ASSIGNEE(S): Smithkline Beecham PLC, UK; Blackburn, Thomas Paul
SOURCE: PCT Int. Appl., 13 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9804289 | A2 | 19980205 | WO 97-EP4159 | 19970722 |
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| RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9742972 | A1 | 19980220 | AU 97-42972 | 19970722 |
| PRIORITY APPLN. INFO.: | | | GB 96-15767 | 19960726 |
| | | | WO 97-EP4159 | 19970722 |

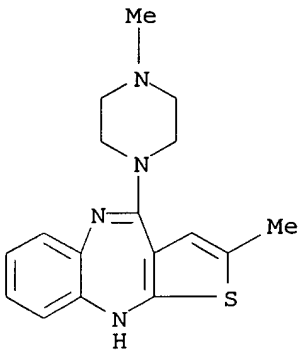
AB Combinations of compds. having 5-HT2C and D2 antagonist activity, compds. having activity at the two receptors, pharmaceutical compns. contg. them, and their use in treating CNS disorders, including schizophrenia, are disclosed.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(D2 antagonist and 5-HT2C antagonist for treatment of CNS disorders, including schizophrenia, and compd. prepn.)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 7 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1998:60037 CAPLUS

DOCUMENT NUMBER: 128:200900

TITLE: Olanzapine attenuates the reinforcing effects of cocaine

AUTHOR(S): Meil, William M.; Schechter, Martin D.

CORPORATE SOURCE: Dep. Pharmacol., Northeastern Ohio Univ. Coll. Med., Rootstown, OH, 44272-0095, USA

SOURCE: Eur. J. Pharmacol. (1997), 340(1), 17-26
CODEN: EJPHAZ; ISSN: 0014-2999

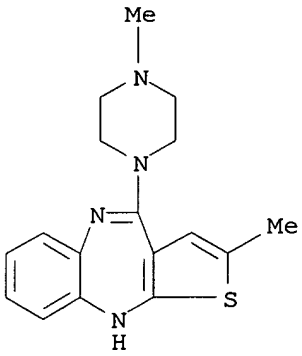
PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The possibility that the atypical neuroleptic olanzapine can antagonize the ability of cocaine to **produce** both conditioned place preference and self-administration in rats was investigated. Pre-treatment with olanzapine (3.0, 4.5 mg/kg, but not 1.5 mg/kg) significantly attenuated conditioned place preference **produced** by cocaine (10 mg/kg). However, the higher dose of olanzapine administered alone resulted in conditioned place aversion. Pre-treatment with olanzapine also **produced** a dose-dependent decrease in cocaine self-administration (0.33 mg/infusion) under a fixed-ratio 2 schedule of reinforcement. Olanzapine **produced** a similar dose-responsive attenuation in operant responding for food (fixed-ratio 10) suggesting that olanzapine **produces** nonspecific decrease in operant behavior. Pre-treatment with 4.5 mg/kg olanzapine significantly attenuated cocaine-induced hyperactivity, whereas lower olanzapine doses had little effect upon cocaine-induced hyperactivity. These results suggest that pre-treatment with olanzapine is capable of blocking the reinforcing effects of cocaine and illustrates the value of using multiple tests of reinforcement when evaluating the pharmacol. effects of newer psychotherapeutic agents.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(olanzapine attenuation of reinforcing effects of cocaine)
RN 132539-06-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



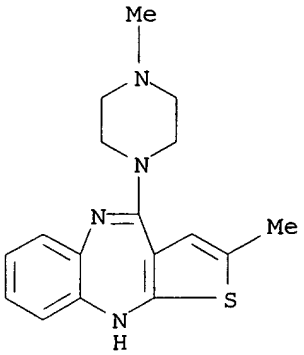

L5 ANSWER 8 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:749549 CAPLUS
DOCUMENT NUMBER: 128:70682
TITLE: Differential regulation of D2 and D4 dopamine receptor mRNAs in the primate cerebral cortex vs. neostriatum: effects of chronic treatment with typical and atypical antipsychotic drugs
AUTHOR(S): Lidow, Michael S.; Goldman-Rakic, Patricia S.
CORPORATE SOURCE: Section of Neurobiology, Yale University School of Medicine, New Haven, CT, USA
SOURCE: J. Pharmacol. Exp. Ther. (1997), 283(2), 939-946
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The RNase Protection Assay was used to examine the regulation of D2 and D4 dopamine receptor mRNAs in the cerebral cortex and neostriatum of nonhuman primates after chronic treatment with a wide spectrum of antipsychotic medications (chlorpromazine, clozapine, haloperidol, molindone, olanzapine, pimozide, remoxipride and risperidone). Tiapride, a D2 antagonist that lacks antipsychotic activity, was also included. All drugs were administered orally for 6 mo at doses recommended for humans. All antipsychotic drug treatments examd. in this study caused a statistically significant up-regulation of both the long and short isoforms of the D2 receptor mRNAs in the prefrontal and temporal cortex. Tiapride, in contrast, significantly up-regulated only the level of D2-long mRNA in these areas. The same drug treatments **produced** less uniform effects in the neostriatum than in the cortex: clozapine and olanzapine failed to significantly elevate either D2-long or D2-short receptor messages in this structure unlike all other drugs,

including tiapride. In both the cerebral cortex and striatum, D4 receptor mRNA was upregulated by certain typical (chlorpromazine and haloperidol) and certain atypical (clozapine, olanzapine and risperidone) antipsychotic agents as well as by tiapride. Other drugs of the typical (molindone and pimozide) and atypical (remoxipride) classes had no effect on D4 mRNA levels in either cortical or striatal tissue. The finding that up-regulation of D2 dopamine receptor mRNAs was a consistently obsd. effect of a wide range of antipsychotic agents in the cerebral cortex but not in the neostriatum, coupled with the fact that the D2-short isoforms in the cortex were not regulated by a non-antipsychotic D2 antagonist, tiapride, draws attention to the importance of the D2 dopamine receptor in the cerebral cortex as a potentially crit., common site of action of antipsychotic medications.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antipsychotics affect on D2 and D4 dopamine receptors in the cerebral cortex and neostriatum)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 9 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:749516 CAPLUS

DOCUMENT NUMBER: 128:70673

TITLE: Phencyclidine-induced deficits in prepulse inhibition of startle are blocked by prazosin, an alpha-1 noradrenergic antagonist

AUTHOR(S): Bakshi, Vaishali P.; Geyer, Mark A.

CORPORATE SOURCE: Department of Neurosciences and Psychiatry, University of California at San Diego, La Jolla, CA, USA

SOURCE: J. Pharmacol. Exp. Ther. (1997), 283(2), 666-674
CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

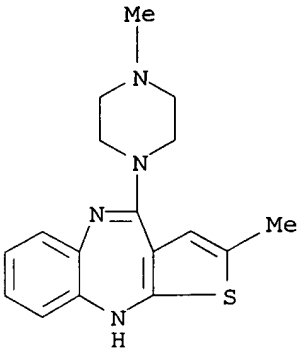
AB Prepulse inhibition (PPI) is a form of plasticity of the startle

response in which presentation of a weak stimulus immediately before an intense starting stimulus reduces the resultant startle response. Deficits in PPI, an operational measure of sensorimotor gating, are obsd. in schizophrenia patients and can be modeled in rats by the psychotogen phencyclidine (PCP). PCP-induced deficits in PPI in rats are resistant to dopamine and serotonin antagonists but can be antagonized by antipsychotics such as clozapine, olanzapine and Seroquel. These latter antipsychotics have antagonistic actions at several receptors, including alpha-1 and alpha-2 adrenergic, M1 muscarinic and .gamma.-aminobutyric acid (GABA)-A receptors. Although the direct actions of PCP are thought to be mediated by noncompetitive antagonism of N-methyl-D-aspartate sites, PCP thereby indirectly activates multiple neurotransmitter systems, including those affected by the aforementioned antipsychotics. The present studies examd. the possibility that an antagonist action at a particular receptor subtype might be responsible for the interaction between PCP and the clozapine-like antipsychotics by testing whether a selective antagonist at alpha-1, alpha-2, M1 or GABA-A receptors would prevent the PCP-induced deficit in PPI in rats. Animals were pretreated with either the alpha-1 antagonist prazosin (0, 0.5, 1.0 or 2.5 mg/kg), the alpha-2 antagonist RX821002 (0, 0.2 or 0.4 mg/kg), the M1 muscarinic antagonist pirenzepine (0, 10 or 30 mg/kg) or the GABA-A antagonist pitrazepin (0, 1.0 or 3.0 mg/kg) and then treated with either saline or PCP (1.5 mg/kg). Because prazosin was effective in blocking the effects of PCP, an addnl. expt. tested the possibility that prazosin (0, 1.0 or 2.5 mg/kg) would block the PPI deficits **produced** by the dopamine agonist apomorphine (0 or 0.5 mg/kg). After drug administration, animals were tested in startle chambers PCP was found repeatedly to decrease PPI. Prazosin (1.0 and 2.5 mg/kg) blocked this deficit in two sep. expts. but did not increase base-line PPI levels. The effects on PPI were dissociable from changes in startle reactivity. Furthermore, prazosin did not antagonize apomorphine-induced disruptions of PPI, which suggests that the antagonism of the PCP effect was not simply due to a generalized improvement of deficient PPI. The antagonists for alpha-2, for M1 and for GABA-A receptors had no effect on base-line PPI or on PCP-induced disruptions in PPI. These findings indicate that the PPI-disruptive effect of PCP may be mediated in part by alpha-1 adrenergic receptors and that antagonism of alpha-1 receptors may play a major role in mediating the blockade of PCP-induced deficits in PPI by certain antipsychotics.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(mechanism of phencyclidine-induced deficits in prepulse inhibition of startle and effects of antipsychotics)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



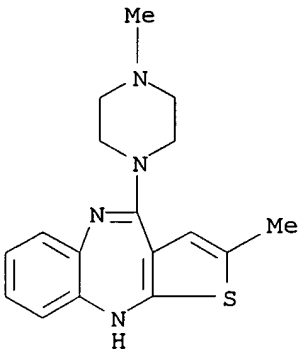
L5 ANSWER 10 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:723639 CAPLUS
DOCUMENT NUMBER: 128:57321
TITLE: Increased food consumption by clozapine, but not by olanzapine, in satiated rats
AUTHOR(S): Benvenga, Mark J.; Leander, J. David
CORPORATE SOURCE: Neuroscience Division, Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Drug Dev. Res. (1997), 41(1), 48-50
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Various drugs used to treat schizophrenia have been repeatedly shown to increase body wt. in both animals and humans. There are different theories as to why this occurs, but the most recently studied theory is that these drugs which cause wt. gain do so because of an antagonist effect at the 5HT2c receptor. In this work, we studied the effects of olanzapine, clozapine, and risperidone on feeding behavior. Over a 4-h test period in satiated rats, clozapine, over a broad dose range, significantly increased food consumption. Similarly, risperidone increased food consumption relative to control. In contrast, olanzapine did not significantly increase food consumption in rats at any dose tested over the 4-h test period. This suggests that olanzapine may be different from clozapine and risperidone with respect to potential wt. gain in schizophrenic patients. Moreover, we believe that the effect **produced** by clozapine and risperidone is due to the alpha-adrenergic activity of these compds., since olanzapine has a much lower affinity for alpha adrenergic receptors than does clozapine or risperidone, and not due to the 5HT2c activity, which all three compds. have in common.

IT **132539-06-1**, Olanzapine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(role of .alpha.-adrenergic and 5-HT2C receptors in effects of atypical antipsychotic drugs on feeding behavior in rats)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 11 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:623040 CAPLUS
DOCUMENT NUMBER: 127:268044
TITLE: Olanzapine for treating autism and mental retardation
INVENTOR(S): Beasley, Charles M., Jr.; Tollefson, Gary D.
PATENT ASSIGNEE(S): Eli Lilly and Company, USA; Beasley, Charles M. Jr.; Tollefson, Gary D.
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9733585 | A1 | 19970918 | WO 96-US19576 | 19961204 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9711501 | A1 | 19971001 | AU 97-11501 | 19961204 |
| PRIORITY APPLN. INFO.: | | | US 96-13162 | 19960311 |
| | | | WO 96-US19576 | 19961204 |

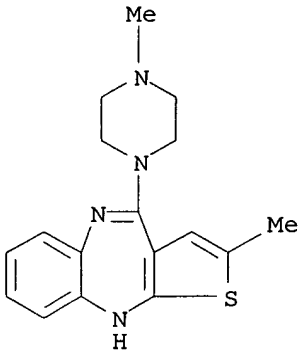
AB The invention provides a method for treating autistic disorder and/or mental retardation comprising administering an effective amt. of olanzapine (I) to a patient in need thereof. I is preferably in Form II polymorph and orally administered. I was suspended in anhyd. EtOAc, heated to 76.degree., cooled to 25.degree., and isolated using vacuum filtration. The **product** was identified as Form II using x-ray powder anal. I was formulated

into tablets.

IT **132539-06-1P**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(olanzapine for treating autism and metal retardation)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 12 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:567794 CAPLUS

DOCUMENT NUMBER: 127:229096

TITLE: Behavioral pharmacology of olanzapine: a novel antipsychotic drug

AUTHOR(S): Moore, Nicholas A.; Leander, J. David; Benvenga, Mark J.; Gleason, Scott D.; Shannon, Harlan

CORPORATE SOURCE: Lilly Research Center Ltd., Eli Lilly and Company, Surrey, GU20 6PH, UK

SOURCE: J. Clin. Psychiatry (1997), 58(Suppl. 10), 37-44
CODEN: JCLPDE; ISSN: 0160-6689

PUBLISHER: Physicians Postgraduate Press

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

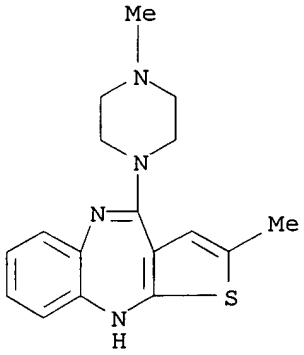
AB This review with 28 refs. describes the behavioral pharmacol. of olanzapine and compares it to its in vitro profile and to clozapine and a no. of other antipsychotic agents, and ests. the likelihood that olanzapine will be an effective and safe antipsychotic with fewer side effects. Since there is no model of schizophrenia, per se, a battery of behavioral assays has been used. Behavioral assays confirm the in vitro results that olanzapine interacts with dopamine, serotonin, and muscarinic receptor subtypes. Moreover, olanzapine appears to have a clozapine-like atypical profile based on (1) mesolimbic selectivity, (2) blocking 5-HT receptors at a lower dose than dopamine receptors, and (3) inhibiting the conditioned avoidance response (indicative of antipsychotic efficacy) at doses that are lower than those required to induce catalepsy (indicative of extrapyramidal side effects). Not only is this profile similar to that of clozapine, but olanzapine has other

similarities: olanzapine substitutes for clozapine in a drug discrimination assay; like clozapine and unlike "typical" antipsychotics, olanzapine increases responding in a conflict procedure; and olanzapine, like clozapine, reverses changes induced by antagonists of the NMDA receptor. On the basis of these findings, we predict that olanzapine will be an efficacious antipsychotic, active against both pos. and neg. symptoms, while **producing** fewer extrapyramidal symptoms than existing treatments.

IT **132539-06-1**, LY170053
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(behavioral pharmacol. of olanzapine, a novel antipsychotic drug)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 13 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:443204 CAPLUS

DOCUMENT NUMBER: 127:70845

TITLE: Antiemetic pharmaceutical compositions containing olanzapine

INVENTOR(S): Van Tran, Pierre

PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA

SOURCE: Brit. UK Pat. Appl., 19 pp.
CODEN: BAXXDU

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| GB 2305860 | A1 | 19970423 | GB 96-6618 | 19960329 |

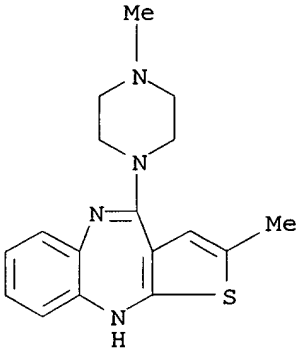
AB Antiemetic pharmaceutical compns. contg. olanzapine (I) are useful in the treatment of emesis, particularly related to chemotherapy. Thus, 270 g sample of tech. grade I (prepn. given) was suspended in 2.7 L anhyd. Et acetate and heated at 76.degree. for 30 min. The mixt was allowed to cool to 25.degree. and the resulting

**product** was isolated and identified as form II using X-ray powder anal. Formulation of I tablets are disclosed.

IT **132539-06-1P**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antiemetic pharmaceutical compns. contg. olanzapine)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 14 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:400460 CAPLUS

DOCUMENT NUMBER: 127:70833

TITLE: Solvate of olanzapine

INVENTOR(S): Larsen, Samuel D.

PATENT ASSIGNEE(S): Eli Lilly and Company, USA; Lilly Industries Ltd.

SOURCE: U.S., 8 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5637584 | A | 19970610 | US 95-410263 | 19950324 |

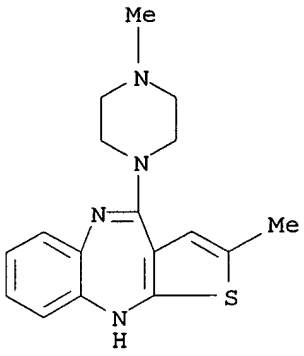
AB A methylene chloride solvate of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (I) which is useful for the desired anhyd. form is provided. Thus, 5.0 g of tech. grade I was suspended in methylene chloride and heated to about 30.degree. for 30 min, then chilled to 5.degree. and the **product** thus obtained was isolated by vacuum filtration.

IT **132539-06-1**, Olanzapine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(solvate of olanzapine)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-

piperazinyl)- (9CI) (CA INDEX NAME)

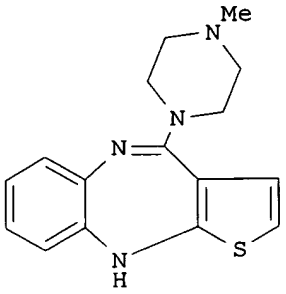



L5 ANSWER 15 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:324780 CAPLUS
DOCUMENT NUMBER: 127:5106
TITLE: **Preparation** of 2-methylthienobenzodiazepine as central nervous system agent.
INVENTOR(S): Chakrabarti, Jiban K.; Hotten, Terrence M.; Tupper, David E.
PATENT ASSIGNEE(S): Lilly Industries Ltd., UK
SOURCE: U.S., 11 pp. Cont.-in-part of U.S. Ser. No. 44,844, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5627178 | A | 19970506 | US 95-387997 | 19950213 |
| US 5229382 | A | 19930720 | US 92-890348 | 19920522 |
| US 5817655 | A | 19981006 | US 96-748292 | 19961113 |
| PRIORITY APPLN. INFO.: | | | US 91-690143 | 19910423 |
| | | | US 92-890348 | 19920522 |
| | | | US 93-44844 | 19930408 |
| | | | GB 90-9229 | 19900425 |
| | | | US 95-387997 | 19950213 |

GI

Applicant's



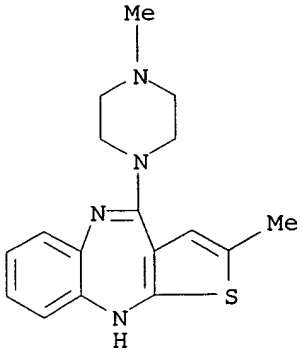
I

AB 2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine (I), or an acid salt thereof, has pharmaceutical properties, and is of particular use in the treatment of disorders of the central nervous system. Compd. I is used in the treatment of schizophrenia, catatonic, delusional disorder, brief reactive psychosis, manic depression, anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder, delusions, hallucinations, and disorganized behavior. Thus, 4.3g of 4-amino-2-methyl-10H-thieno[2,3-b]benzodiazepine hydrochloride (prepn. given) was reluxed in a mixt. of 15 mL of N-methylpiperazine, DMSO, and toluene for 20 h to give 1.65g I. Formulations contg. I were described.

IT **132539-06-1P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-methyl-thieno-benzodiazepine as central nervous system agent)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 16 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:296931 CAPLUS

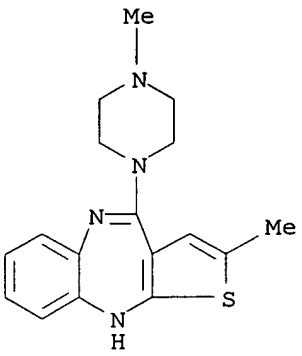
DOCUMENT NUMBER: 126:282829
TITLE: Polyurethane hydrogel drug reservoirs for use in transdermal drug delivery systems
INVENTOR(S): Chen, Tung-Fen; Chiang, Chia-Ming; Jona, Janan; Joshi, Priti; Ramdas, Asha
PATENT ASSIGNEE(S): Cygnus, Inc., USA; Chen, Tung-Fen; Chiang, Chia-Ming; Jona, Janan; Joshi, Priti; Ramdas, Asha
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9709970 | A1 | 19970320 | WO 96-US14739 | 19960913 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG | | | | |
| AU 9671097 | A1 | 19970401 | AU 96-71097 | 19960913 |
| PRIORITY APPLN. INFO.: | | | US 95-528105 | 19950914 |
| | | | US 95-581128 | 19951229 |
| | | | WO 96-US14739 | 19960913 |

AB High capacity drug reservoirs are provided for incorporation into transdermal drug delivery systems. The drug reservoirs are hydrogels formulated from polyurethanes crosslinked with diisocyanate crosslinking agents or cured with radiation in the presence of a photoinitiator. Drug loading as high as 65 to 70 wt.% or higher can be achieved by absorbing drug formulation into the reservoir after hydrogel **synthesis**. Methods for making and using transdermal systems contg. such reservoirs are provided as well. E.g., a hydrogel compn. contains olanzapine, Hypol PreMA G-50, Me laurate lauryl lactate and 1,2-butanediol.

IT **132539-06-1**, Olanzapine
RL: PEP (Physical, engineering or chemical process); POF (Polymer in formulation); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(polyurethane hydrogel drug reservoirs for transdermal drug delivery systems)

RN 132539-06-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 17 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:169159 CAPLUS
DOCUMENT NUMBER: 126:195254
TITLE: Use of .alpha.2-adrenergic drugs to prevent adverse effects of NMDA antagonist- or schizophrenia-associated NMDA receptor hypofunction (NRH)
INVENTOR(S): Olney, John W.; Farber, Nuri B.
PATENT ASSIGNEE(S): Washington University, USA
SOURCE: U.S., 19 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5605911 | A | 19970225 | US 95-381334 | 19950131 |

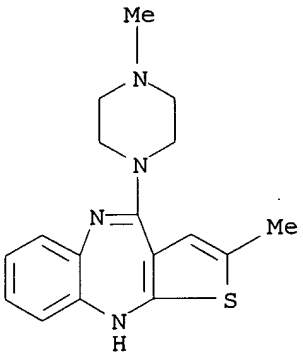
AB Methods and compns. are disclosed for treating or preventing adverse CNS effects **produced** by NMDA receptor hypofunction (NRH), including hypofunction induced by NMDA antagonist drugs, and hypofunction occurring as a causative or aggravating factor in schizophrenia. One method of this invention comprises administering an .alpha.2-adrenergic receptor agonist drug along with an NMDA antagonist drug. The NMDA antagonist drug exerts a primary benefit in reducing excitotoxic brain damage, alleviating neuropathic pain, or preventing or avoiding tolerance or addiction to various types of drugs. The .alpha.2 agonist drug acts as a secondary or "safener" drug, to prevent the neurotoxic side effects that would be caused by the NMDA antagonist in the absence of the safener drug. Another method disclosed herein involves the use of an .alpha.2 agonist drug, by itself, to combat a different and naturally-occurring form of NMDA receptor hypofunction which occurs as a causative or aggravating mechanism in people suffering from schizophrenia. Although .alpha.2 agonists are usually not effective in treating long-standing cases of chronic schizophrenia, where pathol. changes in the brain have already reached or approached maximal levels, .alpha.2 agonists can be administered early in the illness, such as

at the first signs of schizophrenic illness, and continuously or intermittently thereafter to prevent the development or worsening of pathol. brain changes.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antipsychotic drug effect in protection against NMDA receptor hypofunction)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 18 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:84720 CAPLUS

DOCUMENT NUMBER: 126:233631

TITLE: Blockade of phencyclidine-induced hyperlocomotion by olanzapine, clozapine, and serotonin receptor subtype-selective antagonists in mice

AUTHOR(S): Gleason, Scott D.; Shannon, Harlan E.

CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly Company, Indianapolis, IN, 46285, USA

SOURCE: Psychopharmacology (Berlin) (1997), 129(1), 79-84
CODEN: PSCHDL; ISSN: 0033-3158

PUBLISHER: Springer

DOCUMENT TYPE: Journal

LANGUAGE: English

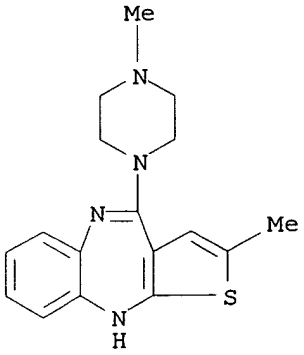
AB In humans, phencyclidine (PCP) is known to **produce** a syndrome of behavioral effects which have many characteristics in common with schizophrenia. Therefore, antagonism of PCP effects might be evidence for antipsychotic efficacy of a compd. The effects of the D2-like antagonist haloperidol, the mixed D2-like/5-HT2 antagonists olanzapine and clozapine, and a series of 5-HT receptor subtype selective antagonists on the hyperlocomotion **produced** by PCP were evaluated in mice. PCP (0.310 mg/kg) **produced** a dose-related increase in locomotor activity, with a peak effect at 3.0 mg/kg. The D2-like antagonist haloperidol **produced** a dose-related decrease in locomotor activity when

administered alone, and blocked the hyperactivity effects of PCP over the same dose-range (minimal ED, MED = 0.3 mg/kg for both effects). In contrast, olanzapine and clozapine reversed the hyperlocomotion effects of PCP at doses (MED = 0.03 and 0.3 mg/kg, resp.) approx. 30- and 10-fold, resp., below those that decreased activity when administered alone (MED = 1.0 and 3.0 mg/kg, resp.). The selective 5-HT2 antagonist LY53857 (0.33.0 mg/kg) administered alone had no effect on locomotor activity but reversed (MED = 0.1 mg/kg) the effects of PCP. Similarly, the selective 5-HT2A/2C antagonist ritanserin (0.0011.0 mg/kg) alone had no effect on locomotor activity, but reversed (MED = 0.01 mg/kg) the effects of PCP. The selective 5-HT2A antagonists ketanserin (MED = 3.0 mg/kg) and MDL 100,907 (MED = 0.3 mg/kg) **produced** dose-related decreases in locomotor activity and ketanserin (MED = 0.1 mg/kg) and MDL 100,907 (MED = 0.003 mg/kg) reversed the effects of PCP. The selective 5-HT3 antagonist zatosetron (0.0110 mg/kg) and the selective 5-H1A antagonist WAY 100,635 (0.0013 mg/kg) were without effects on spontaneous locomotor activity. Zatosetron reversed the effects of 3.0 mg/kg PCR at the nonselective dose of 10 mg/kg whereas WAY 100,635 (0.0011 mg/kg) did not affect PCP-induced hyperlocomotion. The present results indicate that PCP increases locomotor activity, at least in part, due to actions at 5-HT2A, but not 5-HT3 or S-HT1A, receptors. Further, the present findings support the hypothesis that antagonism at 5-HT2A receptors contributes to the in vivo actions of atypical antipsychotics such as olanzapine and clozapine.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blockade of phencyclidine-induced hyperlocomotion by D2 and 5-HT receptor antagonists)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 19 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:63851 CAPLUS

DOCUMENT NUMBER: 126:180769

TITLE: Disposition and biotransformation of the

antipsychotic agent olanzapine in humans

AUTHOR(S): Kassahun, Kelem; Mattiuz, Edward; Nyhart, Eldon, Jr.; Obermeyer, Boyd; Gillespie, Todd; Murphy, Anthony; Goodwin, R. Michael; Tupper, David; Callaghan, J. Thomas; Lemberger, Louis

CORPORATE SOURCE: Department of Drug Metabolism, Lilly Research Laboratories, Eli Lilly and Company, Lilly Research Centre, Indianapolis, IN, 46285, USA

SOURCE: Drug Metab. Dispos. (1997), 25(1), 81-93
CODEN: DMDSAI; ISSN: 0090-9556

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

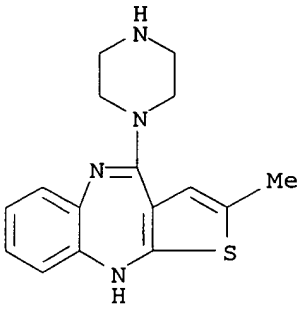
AB Disposition and biotransformation of the new antipsychotic agent olanzapine (OLZ) were studied in six male healthy volunteers after a single oral dose of 12.5 mg contg. 100 .mu.Ci of [14C]OLZ. Biol. fluids were analyzed for total radioactivity, the parent compd. (GC/MS), and metabolites (electrospray LC/MS and LC/MS/MS). Mean radiocarbon recovery was .apprx.87%, with 30% appearing in the feces and 57% excreted in the urine. Approx. half of the radiocarbon was excreted within 3 days, whereas >70% of the dose was recovered within 7 days of dosing. Circulating radioactivity was mostly restricted to the plasma compartment of blood. Mean peak plasma concn. of OLZ was 11 ng/mL, whereas that of radioactivity was 39 ng eq/mL. Mean plasma terminal elimination half-lives were 27 and 59 h, resp., for OLZ and total radioactivity. With the help of NMR and MS data, a major metabolite of OLZ in humans was characterized as a novel tertiary N-glucuronide in which the glucuronic acid moiety is attached to the nitrogen at position 10 of the benzodiazepine ring. Another N-glucuronide was detected in urine and identified as the quaternary N-linked 4'-N-glucuronide. Oxidative metab. on the allylic Me group resulted in 2-hydroxymethyl and 2-carboxylic acid derivs. of OLZ. The Me piperazine moiety was also subject to oxidative attack, giving rise to the N-oxide and N-desmethyl metabolites. Other metabolites, including the N-desmethyl-2-carboxy deriv., resulted from metabolic reactions at both the 4' nitrogen and 2-Me groups. The 10-N-glucuronide and OLZ were the two most abundant urinary components, accounting for .apprx.13% and 7% of the dose, resp. In fecal exts., the only significant radioactive HPLC peaks were due to 10-N-glucuronide and OLZ representing, resp., .apprx.8% and 2% of the administered dose. Semiquant. data obtained from plasma samples from subjects given [14C]OLZ suggest that the main circulating metabolite is 10-N-glucuronide. Thus, OLZ was extensively metabolized in humans via N-glucuronidation, allylic hydroxylation, N-oxidn., N-dealkylation and a combination thereof. The 10-N-glucuronidation pathway was the most important pathway both in terms of contribution to drug-related circulating species and as an excretory **product** in feces and urine.

IT **161696-76-0 186792-77-8 186792-80-3 187454-81-5**
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(disposition and biotransformation of antipsychotic agent olanzapine in humans)

RN 161696-76-0 CAPLUS

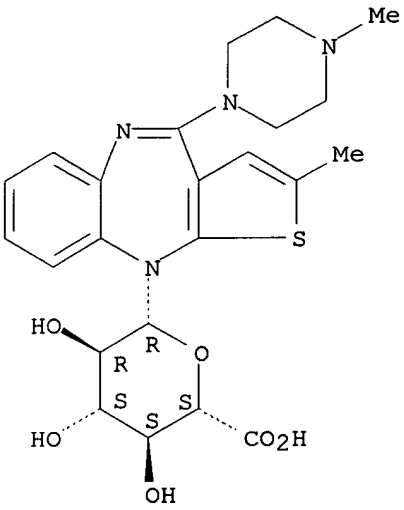
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(1-piperazinyl)-

(9CI) (CA INDEX NAME)

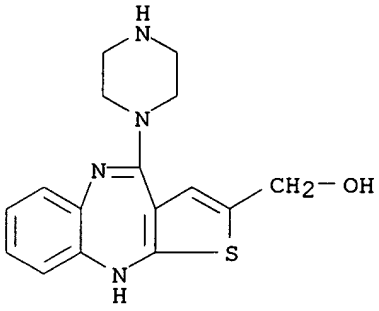


RN 186792-77-8 CAPLUS
RN 186792-80-3 CAPLUS
CN .beta.-D-Glucopyranuronic acid, 1-deoxy-1-[2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepin-10-yl]- (9CI) (CA INDEX NAME)

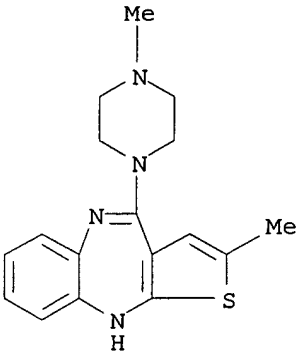
Absolute stereochemistry.



RN 187454-81-5 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine-2-methanol, 4-(1-piperazinyl)- (9CI) (CA INDEX NAME)

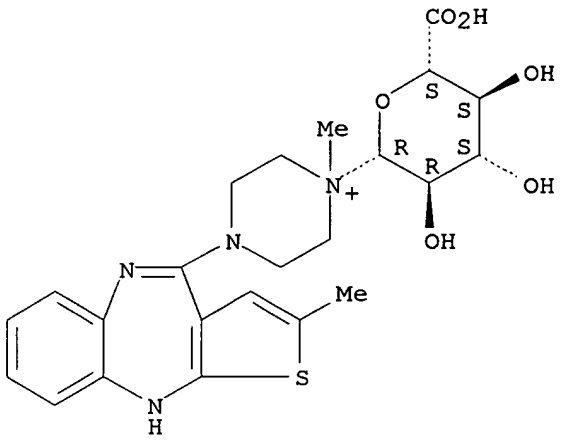


IT **132539-06-1**, Olanzapine
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(disposition and biotransformation of antipsychotic agent olanzapine in humans)
RN 132539-06-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)

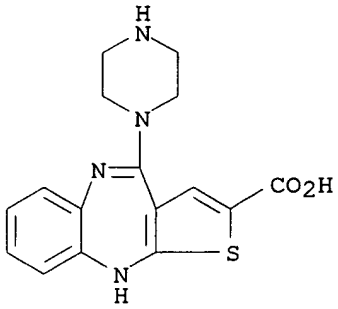


IT **186792-75-6 186792-79-0 187454-79-1 187454-80-4**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(disposition and biotransformation of antipsychotic agent olanzapine in humans)
RN 186792-75-6 CAPLUS
RN 186792-79-0 CAPLUS
CN Piperazinium, 1-.beta.-D-glucopyranuronosyl-1-methyl-4-(2-methyl-10H-thieno[2,3-b][1,5]benzodiazepin-4-yl)- (9CI) (CA INDEX NAME)

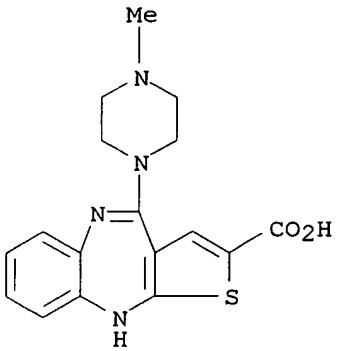
Absolute stereochemistry.



RN 187454-79-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine-2-carboxylic acid, 4-(1-piperazinyl)- (9CI) (CA INDEX NAME)



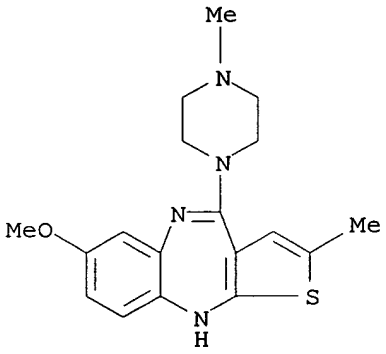
RN 187454-80-4 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine-2-carboxylic acid, 4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 20 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:56315 CAPLUS
DOCUMENT NUMBER: 126:152692
TITLE: The **synthesis** and biological activity of some known and putative metabolites of the atypical antipsychotic agent olanzapine (LY170053)
AUTHOR(S): Calligaro, David O.; Fairhurst, John; Hotten, Terrence M.; Moore, Nicholas A.; Tupper, David E.
CORPORATE SOURCE: Lilly Res. Cent. Ltd., Eli Lilly Co., Surrey, GU20 6PH, UK
SOURCE: Bioorg. Med. Chem. Lett. (1997), 7(1), 25-30
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

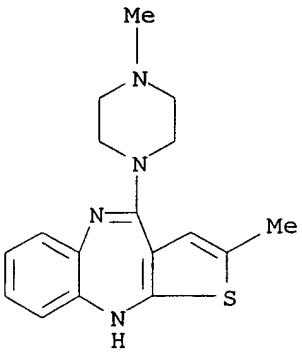
AB 4'-N-desmethyl olanzapine, olanzapine 4'-N-oxide and 2-hydroxymethyl olanzapine have been prepd. and their pharmacol. compared to that of the parent compd. olanzapine. The 4'-N-quaternary glucuronide has also been prepd. All metabolites were significantly less active than olanzapine in the tests conducted: binding to neuronal receptors, apomorphine-induced climbing behavior in mice and conditioned avoidance behavior in rats.

IT **186792-76-7 186792-81-4**
RL: RCT (Reactant)
(reactant; **synthesis** and biol. activity of known and putative metabolites of antipsychotic agent olanzapine)
RN 186792-76-7 CAPLUS
RN 186792-81-4 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-methoxy-2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)

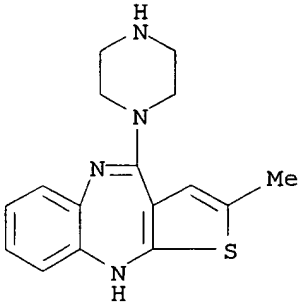



IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**synthesis** and biol. activity of known and putative

metabolites of antipsychotic agent olanzapine)
RN 132539-06-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



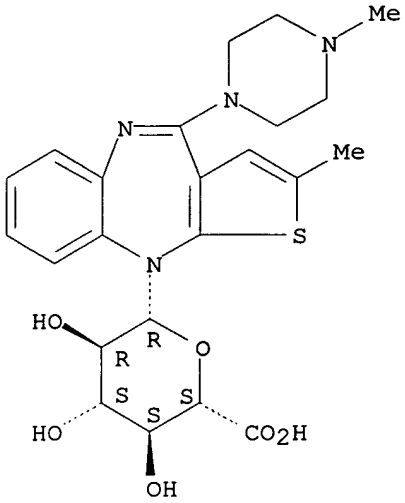
IT **186792-77-8P**
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); USES (Uses)
(**synthesis** and biol. activity of known and putative metabolites of antipsychotic agent olanzapine)
RN 186792-77-8 CAPLUS
IT **161696-76-0P 186792-75-6P 186792-80-3P**
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); USES (Uses)
(**synthesis** and biol. activity of known and putative metabolites of antipsychotic agent olanzapine)
RN 161696-76-0 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(1-piperazinyl)- (9CI) (CA INDEX NAME)



RN 186792-75-6 CAPLUS
RN 186792-80-3 CAPLUS

CN .beta.-D-Glucopyranuronic acid, 1-deoxy-1-[2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepin-10-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

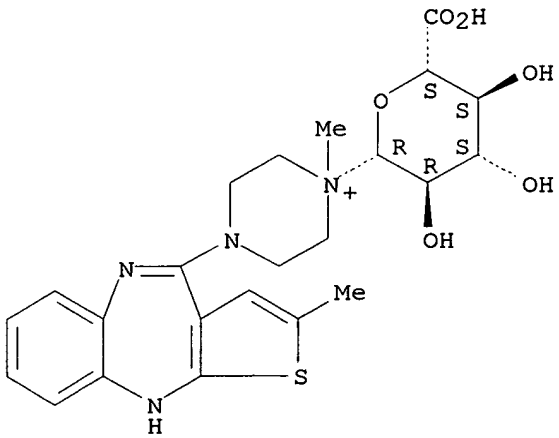


IT **186792-79-0P 186792-83-6P 186792-95-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(**synthesis** and biol. activity of known and putative metabolites of antipsychotic agent olanzapine)

RN 186792-79-0 CAPLUS

CN Piperazinium, 1-.beta.-D-glucopyranuronosyl-1-methyl-4-(2-methyl-10H-thieno[2,3-b][1,5]benzodiazepin-4-yl)- (9CI) (CA INDEX NAME)

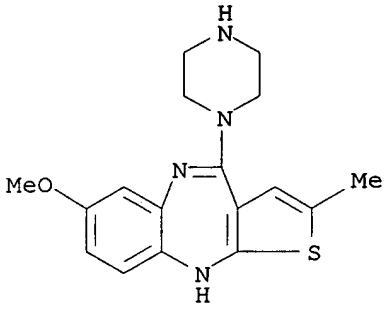
Absolute stereochemistry.



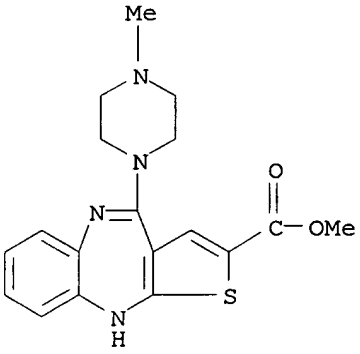
RN 186792-83-6 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-methoxy-2-methyl-4-(1-

piperazinyl)- (9CI) (CA INDEX NAME)



RN 186792-95-0 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine-2-carboxylic acid, 4-(4-methyl-1-piperazinyl)-, methyl ester (9CI) (CA INDEX NAME)



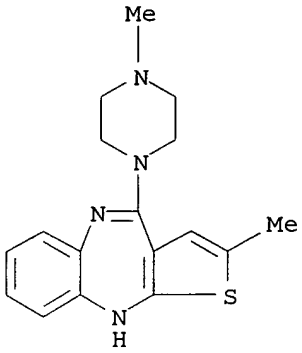
L5 ANSWER 21 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:734646 CAPLUS
DOCUMENT NUMBER: 126:14642
TITLE: Effects of typical and atypical antipsychotic drugs on freezing behavior induced by conditioned fear
AUTHOR(S): Inoue, Takeshi; Tsuchiya, Kiyoshi; Koyama, Tsukasa
CORPORATE SOURCE: Dep. of Phychiatry, Hokkaido Univ. Sch. of Medicine, Sapporo, 060, Japan
SOURCE: Pharmacol., Biochem. Behav. (1996), 55(2), 195-201
CODEN: PBBHAU; ISSN: 0091-3057
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Atypical antipsychotic drugs (atypical APDs), such as clozapine, ORG 5222, and olanzapine, have been suggested to possess anxiolytic activity in the conflict test and elevated plus-maze test, while

several studies have suggested that typical APDs are not anxiolytic in several models of anxiety. The effects of typical and atypical APDs on the acquisition and expression of conditioned fear-induced freezing were investigated. The drugs were administered s.c. to male Sprague-Dawley rats 30 min before foot-shock stress. Twenty-four hours after foot shock, freezing behavior of rats was obsd. in the shock chamber without shocks. The atypical APD clozapine (0.3-10 mg/kg) dose-dependently inhibited the acquisition of conditioned freezing. Candidates for atypical APDs, ORG 5222 (0.1-1 mg/kg), olanzapine (1-10 mg/kg), and raclopride (3-30 mg/kg), also dose-dependently reduced the acquisition of conditioned freezing. The typical APDs haloperidol (3 mg/kg), spiperone (0.1-1 mg/kg) and nemonapride (1 mg/kg) inhibited the acquisition of conditioned freezing, but their effects were reduced at higher doses. Chlorpromazine, a typical APD, **produced** about 50% inhibition of the acquisition of conditioned freezing only at the dose of 10 mg/kg. The ED50 values (mg/kg) for inhibiting the acquisition of conditioned freezing was correlated with the Ki values for D4 dopaminergic receptors, but not with the ki values for other monoamine and acetylcholine receptors. On the other hand, clozapine or haloperidol did not change the expression of conditioned freezing. The protective effects of clozapine and other antipsychotic drugs on the acquisition of conditioned freezing may be mediated by blockade of D4 receptors.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(freezing behavior induced by conditioned fear response to)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 22 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1996:656468 CAPLUS

DOCUMENT NUMBER: 125:301028

TITLE: **Preparation** of olanzapine solvates

INVENTOR(S): Bunnell, Charles Arthur; Hendriksen, Barry Arnold; Hotten, Terrence Michael; Larsen, Samuel Dean; Tupper, David Edward

PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA; Lilly Industries Ltd.
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

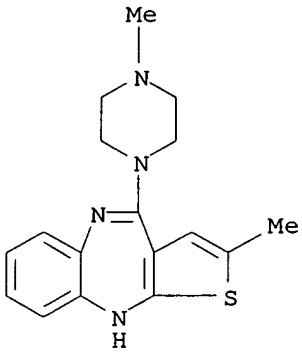
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 733634 | A1 | 19960925 | EP 96-301999 | 19960322 |
| R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| US 5631250 | A | 19970520 | US 95-410474 | 19950324 |
| US 5703232 | A | 19971230 | US 96-586431 | 19960116 |
| WO 9630374 | A1 | 19961003 | WO 96-US3854 | 19960322 |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI | | | | |
| RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9652578 | A1 | 19961016 | AU 96-52578 | 19960322 |
| AU 9654279 | A1 | 19961016 | AU 96-54279 | 19960322 |
| GB 2313835 | A1 | 19971210 | GB 97-19819 | 19960322 |
| GB 2313835 | B2 | 19980916 | | |
| DE 19681286 | T | 19980402 | DE 96-19681286 | 19960322 |
| BR 9607790 | A | 19980707 | BR 96-7790 | 19960322 |
| SE 9703205 | A | 19970905 | SE 97-3205 | 19970905 |
| NO 9704365 | A | 19970922 | NO 97-4365 | 19970922 |
| FI 9703750 | A | 19970922 | FI 97-3750 | 19970922 |
| DK 9701089 | A | 19971112 | DK 97-1089 | 19970923 |
| PRIORITY APPLN. INFO.: | | | US 95-409566 | 19950324 |
| | | | US 95-410474 | 19950324 |
| | | | WO 96-US3854 | 19960322 |
| | | | WO 96-US3917 | 19960322 |

AB The invention provides MeOH, EtOH, and PrOH solvates of olanzapine with improved properties characterized by x-ray spectra.

IT **132539-06-1P**, Olanzapine
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of olanzapine solvates)

RN 132539-06-1 CAPLUS

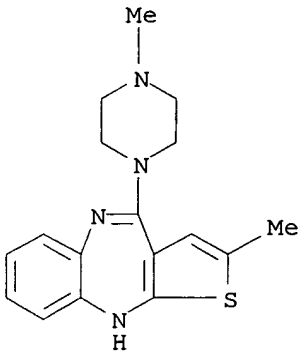
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



IT **182808-49-7P 182808-50-0P 182808-51-1P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of olanzapine solvates)
RN 182808-49-7 CAPLUS
CN Methanol, compd. with 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 132539-06-1
CMF C17 H20 N4 S



CM 2

CRN 67-56-1
CMF C H4 O

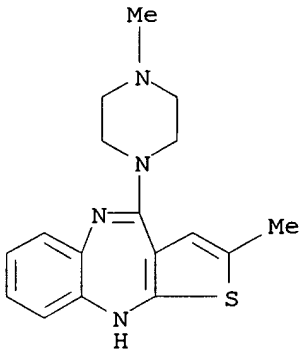
$H_3C-OH$

RN 182808-50-0 CAPLUS

CN Ethanol, compd. with 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 132539-06-1
CMF C17 H20 N4 S



CM 2

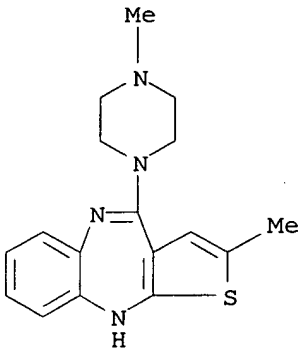
CRN 64-17-5
CMF C2 H6 O

$H_3C-CH_2-OH$

RN 182808-51-1 CAPLUS
CN 1-Propanol, compd. with 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 132539-06-1
CMF C17 H20 N4 S



CM 2

CRN 71-23-8
CMF C3 H8 O

$H_3C-CH_2-CH_2-OH$

L5 ANSWER 23 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:644040 CAPLUS
DOCUMENT NUMBER: 125:275918
TITLE: **Preparation** of crystalline olanzapine
INVENTOR(S): Bunnell, Charles Arthur; Hendriksen, Barry Arnold; Larsen, Samuel Dean
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA; Lilly Industries Ltd.
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 733635 | A1 | 19960925 | EP 96-302000 | 19960322 |
| R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE | | | | |
| WO 9630375 | A1 | 19961003 | WO 96-US3917 | 19960322 |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI | | | | |
| RW: KE, LS, MW, SD, SZ, UG, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| CA 2214005 | AA | 19961003 | CA 96-2214005 | 19960322 |
| AU 9652578 | A1 | 19961016 | AU 96-52578 | 19960322 |
| AU 9654279 | A1 | 19961016 | AU 96-54279 | 19960322 |

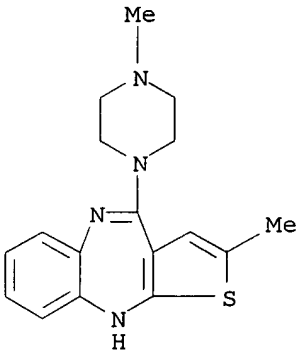
| | | | | |
|---|---|---|---|---|
| GB 2313835 | A1 | 19971210 | GB 97-19819 | 19960322 |
| GB 2313835 | B2 | 19980916 | | |
| DE 19681286 | T | 19980402 | DE 96-19681286 | 19960322 |
| BR 9607790 | A | 19980707 | BR 96-7790 | 19960322 |
| SE 9703205 | A | 19970905 | SE 97-3205 | 19970905 |
| LV 12018 | B | 19980920 | LV 97-163 | 19970908 |
| LT 4349 | B | 19980525 | LT 97-148 | 19970916 |
| NO 9704365 | A | 19970922 | NO 97-4365 | 19970922 |
| FI 9703750 | A | 19970922 | FI 97-3750 | 19970922 |
| DK 9701089 | A | 19971112 | DK 97-1089 | 19970923 |
| PRIORITY APPLN. INFO.: | | | US 95-409566 | 19950324 |
| | | | US 95-410474 | 19950324 |
| | | | WO 96-US3854 | 19960322 |
| | | | WO 96-US3917 | 19960322 |

AB The invention provides a pharmaceutically elegant stable polymorph of olanzapine by pptn. from EtOAc.

IT **132539-06-1P**, Olanzapine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of cryst. olanzapine)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 24 OF 35 CAPLUS COPYRIGHT 1999 ACS

| | |
|---|---|
| ACCESSION NUMBER: | 1996:307170 CAPLUS |
| DOCUMENT NUMBER: | 125:1202 |
| TITLE: | Similarity of clozapine's and olanzapine's acute effects on rats' lapping behavior |
| AUTHOR(S): | Das, Shyamal; Fowler, Stephen C. |
| CORPORATE SOURCE: | Dep. Pharm., Toxicol., Univ. Kansas, Lawrence, KS, 66045, USA |
| SOURCE: | Psychopharmacology (Berlin) (1996), 123(4), 374-378<br>CODEN: PSCHDL; ISSN: 0033-3158 |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |

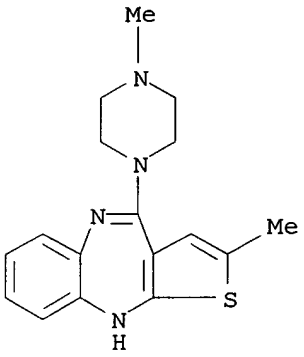
AB As a way of further comparing the behavioral effects of clozapine and olanzapine, dose ranges of these drugs were studied in a task

emphasizing fine motor detail fo rats' tongue movements during lapping behavior. Rats lapped drops of tap water from a force-sensing disk. From this behavior four variables were derived: of sep. tongue contacts in 2 min, and the rhythm of the lapping behavior as quantified by Fourier anal. Both clozapine (0.5-4.0 mg/kg, IP, 45 min) and olanzapine (0.25-2.0 mg/kg, IP, 45 min) dose dependently reduced all four measures of behavior. With respect to lick rhythm, a behavioral marker which clearly distinguishes haloperidol from clozapine in this behavioral paradigm, olanzapine was about twice as potent as clozapine, with the two drugs having parallel dose-effect functions. Within session decrements in behavior previously reported for haloperidol in the lick task were not **produced** by clozapine nor by olanzapine. Taken together, these data strengthen the idea that the behavioral effects of clozapine and olanzapine are strikingly similar, and thereby emphasize the potential of olanzapine as a atypical antipsychotic agent.

IT **132539-06-1**, Olanzapine
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(similarity of clozapine and olanzapine effects on lapping behavior in rats)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 25 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1996:138441 CAPLUS

DOCUMENT NUMBER: 124:250585

TITLE: Effects of olanzapine on regional c-fos expression in rat forebrain

AUTHOR(S): Robertson, George S.; Fibiger, H. Christian

CORPORATE SOURCE: Faculty Medicine, University Ottawa, Ottawa, ON, Can.

SOURCE: Neuropsychopharmacology (1996), 14(2), 105-10
CODEN: NEROEW; ISSN: 0893-133X

DOCUMENT TYPE: Journal

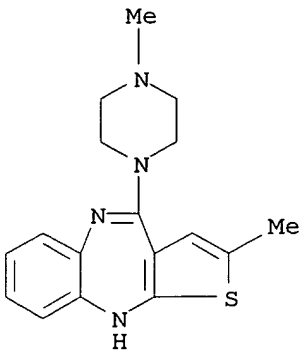
LANGUAGE: English

AB Compared to typical antipsychotic drugs, clozapine **produces** a unique pattern of Fos-like immunoreactive neurons in the rat forebrain. It has been proposed, therefore, that this approach may be useful in identifying other agents with clozapine's therapeutic profile. In the present study, the authors examd. the ability of olanzapine to increase the no. of Fos-like immunoreactive neurons in the striatum, nucleus accumbens, lateral septal nucleus, and prefrontal cortex. Olanzapine (5, 10 mg/kg) **produced** dose-dependent increases in the no. of Fos-pos. neurons in the nucleus accumbens and lateral septal nucleus, important components of the limbic system that may mediate some of the therapeutic actions of neuroleptics. Olanzapine also **produced** dose-dependent increases in the no. of Fos-pos. neurons in the dorsolateral striatum, an effect that correlates with the ability of neuroleptics to **produce** extrapyramidal side-effects. The effects of olanzapine on regional c-fos expression are not therefore identical to clozapine, which is without effect in the dorsolateral striatum. However, olanzapine-induced increases in the dorsolateral striatum were considerably smaller than those generated in the nucleus accumbens suggesting that at low, potentially therapeutic doses olanzapine may not generate significant extrapyramidal side effects. Olanzapine also increased the no. of Fos-pos. neurons in medical prefrontal cortex, an action unique to clozapine and a few other atypical antipsychotics. These findings are consistent with the hypothesis that olanzapine is an atypical antipsychotic in the sense that it does not **produce** significant extrapyramidal side-effects at low therapeutic doses. However, extrapyramidal side-effects at higher doses can be predicted by these results. Finally, olanzapine's actions in the medial prefrontal cortex may be predictive of a clozapine-like profile with respect to actions on neg. symptoms in schizophrenia. Addnl. clin. experience with olanzapine and other new antipsychotics is required to test the validity of these hypotheses.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of olanzapine on regional c-fos gene expression in rat forebrain)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)

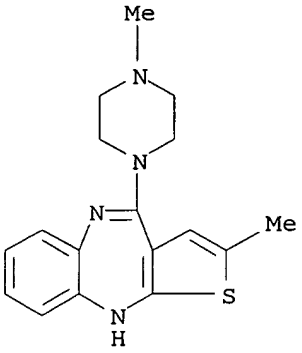


L5 ANSWER 26 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1995:1000944 CAPLUS
DOCUMENT NUMBER: 124:76355
TITLE: Antagonism of phencyclidine-induced deficits in prepulse inhibition by the putative atypical antipsychotic olanzapine
AUTHOR(S): Bakshi, Vaishali P.; Geyer, Mark A.
CORPORATE SOURCE: Departments Neurosciences Psychiatry, University California San Diego, La Jolla, CA, 92093-0804, USA
SOURCE: Psychopharmacology (Berlin) (1995), 122(2), 198-201
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prepulse inhibition (PPI) of the startle reflex provides an operational measure of sensorimotor gating. Deficits in PPI are obsd. in schizophrenia patients and can be modelled in animals by administration of noncompetitive NMDA antagonists such as phencyclidine (PCP) or dizocilpine (MK-801). Previous studies indicate that the atypical antipsychotic clozapine restores PPI in PCP-treated animals while the typical antipsychotic haloperidol does not. Olanzapine (LY170053) is a novel putative atypical antipsychotic that shares many pharmacol. and behavioral properties with clozapine. The present study assessed the ability of olanzapine (0, 1.25, 2.5, 5.0 or 10.0 mg/kg) to antagonize deficits in PPI **produced** by PCP (1.5 mg/kg) and dizocilpine (0.1 mg/kg). At the two highest doses, olanzapine significantly increased PPI in PCP- and dizocilpine-treated animals without affecting PPI or baseline startle reactivity by itself. These results support the notion that olanzapine is functionally similar to clozapine and may have utility as an atypical antipsychotic agent.

IT **132539-06-1**, Olanzapine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(olanzapine effect on startle reflex prepulse inhibition in relation to activity as atypical antipsychotic agent)
RN 132539-06-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-

piperazinyl)- (9CI) (CA INDEX NAME)



L5 ANSWER 27 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1995:768898 CAPLUS
DOCUMENT NUMBER: 123:188398
TITLE: Catalepsy as a rodent model for detecting antipsychotic drugs with extrapyramidal side effect liability
AUTHOR(S): Hoffman, D. C.; Donovan, H.
CORPORATE SOURCE: Neurogen Corporation, CT, 06405, USA
SOURCE: Psychopharmacology (Berlin) (1995), 120(2), 128-33
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English

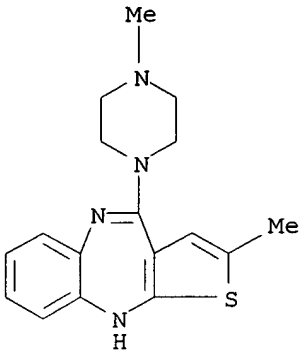
AB The predictive validity of catalepsy as a rodent model for detecting the extrapyramidal side effects (EPS) of antipsychotic drugs was recently questioned when the novel antipsychotic savoxepine **produced** little catalepsy in rodents while **producing** significant EPS in schizophrenic patients. Because catalepsy is viewed as an important model for predicting EPS, we decided to re-evaluate the effects of savoxepine. Savoxepine, clozapine, haloperidol, olanzapine, ORG 5222, raclopride, and risperidone were examd. in two tests for catalepsy (grid and bar tests) in male Sprague-Dawley rats. The ability to antagonize amphetamine-induced hypermotility was also examd., since this measure is believed to predict clin. efficacy. With the exception of clozapine, all drugs **produced** dose-dependent catalepsy in both tests. For each drug, the min. ED for **producing** catalepsy was greater than or equal to the ED50 for antagonizing amphetamine-induced hyperactivity (defined as the dose-**producing** a 50% redn. in hyperactivity). Clozapine resulted in the widest sepn. of EDs in the catalepsy and activity models. Raclopride **produced** the next largest sepn. while the remaining drugs resulted in only a one- or two-fold dose sepn. between the two behavioral tests. The results with haloperidol and clozapine are consistent with the clin. effects of these drugs (severe vs. mild EPS). The ratios of EDs in catalepsy and activity for the remaining novel drugs are also consistent with preliminary clin. findings indicating some EPS with

each of these compds. Thus, catalepsy remains a suitable rodent model for detecting compds. with EPS liability in humans.

IT **132539-06-1**, Olanzapine
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(catalepsy as rodent model for detecting antipsychotic drugs with extrapyramidal side effect liability)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 28 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1995:752833 CAPLUS

DOCUMENT NUMBER: 123:160733

TITLE: Antipsychotic agents antagonize non-competitive N-methyl-D-aspartate antagonist-induced behaviors

AUTHOR(S): Corbett, R.; Camacho, F.; Woods, A. T.; Kerman, L. L.; Fishkin, R. J.; Brooks, K.; Dunn, R. W.

CORPORATE SOURCE: Dep. Biol. Res., Hoechst-Roussel Pharmaceuticals Inc., Somerville, NJ, 08876, USA

SOURCE: Psychopharmacology (Berlin) (1995), 120(1), 67-74
CODEN: PSCHDL; ISSN: 0033-3158

DOCUMENT TYPE: Journal

LANGUAGE: English

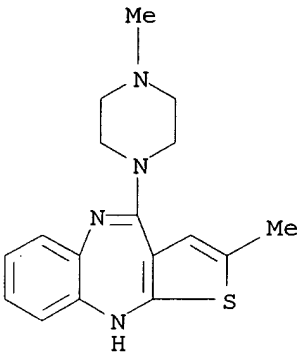
AB Antipsychotic agents were tested for their ability to antagonize both dopaminergic-induced and non-competitive N-methyl-D-aspartate (NMDA) antagonist-induced behaviors. All of the agents dose-dependently antagonized the apomorphine-induced climbing mouse assay (CMA) and dizocilpine (MK-801)-induced locomotion and falling assay (MK-801-LF) with a CMA/MK-801-LF ratio of less than or equal to 1.6. However, clozapine and its structural analog olanzapine more potently antagonized MK-801-LF (1.1 and 0.05 mg/kg) than the CMA (12.3 and 0.45 mg/kg) and as a result had a CMA/MK-801-LF ratio of 11.2 and 9, resp. Furthermore, phencyclidine (PC) (2 mg/kg) can selectively induced social withdrawal in naive rats that were house in pairs (familiar) for 10 days prior to testing without affecting motor activity. SCH 23390, raclopride, haloperidol, chlorpromazine

and risperidone failed to reverse the social withdrawal induced by PCP up to doses which **produced** significant motor impairment. However, clozapine (2.5 and 5.0 mg/kg) and olanzapine (0.25 and 0.5 mg/kg) significantly reversed this social withdrawal in rats. Therefore, the non-competitive NMDA antagonists PCP and MK-801 can induce behaviors in Rodents which are selectively antagonized by clozapine and olanzapine. Furthermore, assessment of the effect of antipsychotic agents in the CMA, MK-801-LF and PCP-induced social withdrawal assays may provide a preclin. approach to identify novel agents for neg. symptoms and treatment resistant schizophrenia.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antipsychotic agents antagonize non-competitive NMDA antagonist-induced behaviors)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 29 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1995:466936 CAPLUS

DOCUMENT NUMBER: 122:230659

TITLE: Olanzapine moderately increases conflict responding but does not **produce** a benzodiazepine-like cue in rat

AUTHOR(S): Nanry, Kevin P.; Pollard, Gerald T.; Howard, James L.

CORPORATE SOURCE: Pharmacology Division, Burroughs Wellcome Co., Research Traingle Park, NC, USA

SOURCE: Drug Dev. Res. (1995), 34(3), 317-19
CODEN: DDREDK; ISSN: 0272-4391

DOCUMENT TYPE: Journal

LANGUAGE: English

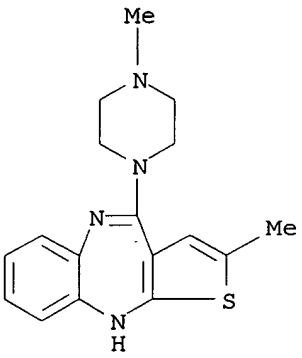
AB In rats pressing a lever for food on a Geller-Seifter conflict schedule with incremental elec. stimulus, the putative novel antipsychotic olanzapine (0.78 and 1.56 mg/kg p.o.) increased conflict responding by 35% (half the maximal increase **produced** by chlordiazepoxide). In rats trained to

discriminate between chlordiazepoxide and saline, olanzapine (0.19-1.56 mg/kg p.o.) reduced response rate dose-dependently; all rats chose the saline-appropriate lever at all doses. The results replicate the moderate anticonflict effect of olanzapine and show that the subjective cue differs from that of a benzodiazepine. A possible anxiolytic action of this class of antipsychotics is proposed.

IT **132539-06-1**, Olanzapine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(olanzapine moderately increases conflict responding but does not **produce** a benzodiazepine-like cue in rat)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 30 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1994:465597 CAPLUS

DOCUMENT NUMBER: 121:65597

TITLE: Sustained-release microsphere containing antipsychotic and process for **producing** the same

INVENTOR(S): Kino, Shigemi; Osajima, Tomonori; Mizuta, Hiroaki

PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical Industries, Ltd., Japan

SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9410982 | A1 | 19940526 | WO 93-JP1673 | 19931115 |
| W: CA, JP, KR, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2148823 | AA | 19940526 | CA 93-2148823 | 19931115 |

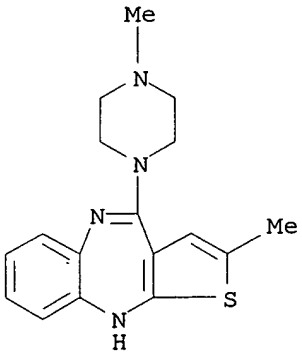
EP 669128 A1 19950830 EP 93-924827 19931115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
US 5656299 A 19970812 US 95-443021 19950517
PRIORITY APPLN. INFO.: JP 92-332441 19921117
WO 93-JP1673 19931115

AB A sustained-release microsphere **produced** by enclosing a hydrophobic antipsychotic such as bromperidol or haloperidol in a base comprising a biocompatible polymer such as polylactic acid or a lactic acid/glycolic acid copolymer. It can exhibit a desired pharmacol. effect, where a long-term administration is necessary, by injecting once every 1 to 8 wk instead of every day. As a result, a remarkable improvement can be expected in the compliance during maintenance therapy. In addn., the use of the biocompatible polymer serves to entirely dispense with surgical operations such as implantation, facilitates hypodermic and i.m. injection just like the case of suspending injection, and can dispense with the withdrawal of the microsphere. Furthermore, the microsphere can be administered with little aversion and pain.

IT **132539-06-1P**, Olanzapine
RL: PREP (Preparation)
(Sustained-release microspheres, manuf. of, biocompatible polymers in)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 31 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1993:662437 CAPLUS

DOCUMENT NUMBER: 119:262437

TITLE: Dependence study on LY170053 in rhesus monkeys and rats

AUTHOR(S): Ando, Kiyoshi; Kawaguchi, Takeshi; Kawakami, Yoshiyuki; Yanagita, Tomoji

CORPORATE SOURCE: Div. Pharmacol., Preclin. Res. Lab., Inc., Kawasaki, 216, Japan

SOURCE: Jitchuken Zenrinsho Kenkyuho (1993), 19(2), 73-92
CODEN: JZKEDZ; ISSN: 0385-8502

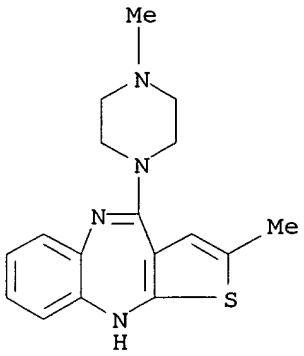
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB The dependence potential of LY170053 (I) was assessed by gross behavior observation (GBO), suppression expt. of barbital withdrawal signs (WDS), and drug self-administration (SA) expt. in rhesus monkeys and GBO and phys. dependence-**producing** expt. (PDPE) in rats. Diazepam (II) was used as a ref. drug. I showed acute depressive effects on the central nervous system (CNS) in both the animals although the effects of I were not the same as those of II. I at 1-8 mg/kg orally did not suppress barbital WDS, whereas II at 8 and 16 mg/kg orally did. In PDPE, I and II were orally given 0.05-0.4 mg and 2-8 mg/g food. resp., for 4 wk. WDS in the I groups were not so marked as those in the II groups although the daily food intake and the body wt. slightly decreased in the I groups during the withdrawal period. SA of I at 0.06, 0.25, and 1 mg/kg/infusion was obsd. in 4 monkeys. None of them showed stable and high rates of SA of I at the above unit doses. These results suggest that I has the acute CNS-depressing effect and that its reinforcing effect in monkeys is very weak if any.

IT **132539-06-1**, LY170053
RL: BIOL (Biological study)
(dependence study of)

RN 132539-06-1 CAPLUS

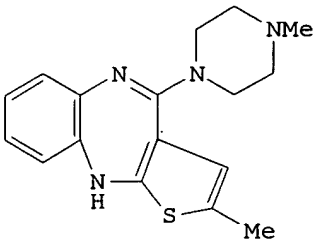
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 32 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1992:584704 CAPLUS
DOCUMENT NUMBER: 117:184704
TITLE: The behavioral pharmacology of olanzapine, a novel "atypical" antipsychotic agent
AUTHOR(S): Moore, Nicholas A.; Tye, Nicholas C.; Axton, Michele S.; Risius, Francesca C.
CORPORATE SOURCE: Lilly Res. Cent., Eli Lilly and Co., Windlesham/Surrey, UK
SOURCE: J. Pharmacol. Exp. Ther. (1992), 262(2), 545-51
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

GI



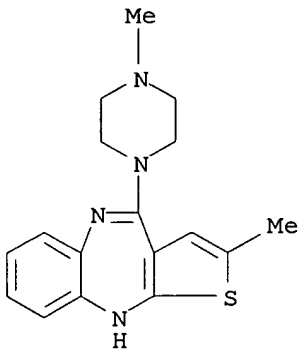

I

AB Olanzapine (LY170053, I) is a novel "atypical" antipsychotic agent with 5-hydroxytryptamine2.dopamine D1/D2 antagonist activity and anticholinergic properties. In behavioral studies, I (1.25-10 mg/kg, p.o.) antagonizes apomorphine-induced climbing behavior in mice, demonstrating that the compd. possesses D1/D2 antagonist activity in vivo. I (0.3-20 mg/kg, oral) antagonizes 5-hydroxytryptophan-induced head twitches in mice at doses much lower than those required to block the climbing response, confirming that in vivo, the compd. is a more potent 5-hydroxytryptamine2 antagonist than dopamine antagonist. I (2.5-10 mg/kg, p.o.) also antagonized oxotremorine-induced tremor in mice. In a conditioned avoidance paradigm in rats, I inhibits the avoidance response with an ED50 of 4.7 mg/kg oral; however, unlike other antipsychotic agents, catalepsy is only obsd. at much higher doses (ED50 39.4 mg/kg, oral). These data would suggest that the compd. will be less likely to **produce** undesirable extrapyramidal symptoms. Unlike "typical" antipsychotics, I (1.25-5 mg/kg oral) increases responding during the conflict component of a modified Geller Seifter test, demonstrating that the compd. may also possess anxiolytic activity. In another series of expts., I (1.25 mg/kg, i.p.) **produced** clozapine-appropriate responding in a drug discrimination model in which animals had been trained to discriminate clozapine (5 mg/kg, i.p.) from vehicle. On the basis of these results, it would therefore be predicted that I will have an atypical profile and will be less likely to induce undesirable extrapyramidal symptoms than currently available drugs.

IT **132539-06-1**, LY 170053
RL: BIOL (Biological study)
(as atypical antipsychotic, behavioral pharmacol. of)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 33 OF 35 CAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1992:83703 CAPLUS
DOCUMENT NUMBER: 116:83703
TITLE: **Preparation** of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno-[2,3-b][1,5]benzodiazepine
INVENTOR(S): Chakrabarti, Jiban Kumar; Hotten, Terrence Michael; Tupper, David Edward
PATENT ASSIGNEE(S): Lilly Industries Ltd., UK
SOURCE: Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 454436 | A1 | 19911030 | EP 91-303679 | 19910424 |
| EP 454436 | B1 | 19950913 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| AU 9175186 | A1 | 19911107 | AU 91-75186 | 19910422 |
| AU 643267 | B2 | 19931111 | | |
| IL 97912 | A1 | 19951031 | IL 91-97912 | 19910422 |
| FI 9101986 | A | 19911026 | FI 91-1986 | 19910424 |
| CA 2041113 | AA | 19911026 | CA 91-2041113 | 19910424 |
| CA 2041113 | C | 19980714 | | |
| NO 9101624 | A | 19911028 | NO 91-1624 | 19910424 |
| NO 178766 | B | 19960219 | | |
| NO 178766 | C | 19960529 | | |
| CN 1056693 | A | 19911204 | CN 91-103346 | 19910424 |
| CN 1028429 | B | 19950517 | | |
| HU 60503 | A2 | 19920928 | HU 91-1372 | 19910424 |
| HU 212416 | B | 19960628 | | |
| ZA 9103085 | A | 19921230 | ZA 91-3085 | 19910424 |
| JP 07089965 | A2 | 19950404 | JP 91-228215 | 19910424 |
| JP 2527860 | B2 | 19960828 | | |
| CZ 279937 | B6 | 19950913 | CZ 91-1168 | 19910424 |
| ES 2078440 | T3 | 19951216 | ES 91-303679 | 19910424 |

| | | | | |
|---|---|---|---|---|
| RU 2043992 | C1 | 19950920 | RU 92-5052762 | 19920925 |
| LV 10262 | B | 19950420 | LV 93-517 | 19930608 |
| FI 9701316 | A | 19970327 | FI 97-1316 | 19970327 |
| PRIORITY APPLN. INFO.: | | | GB 90-9229 | 19900425 |
| | | | FI 91-1986 | 19910424 |

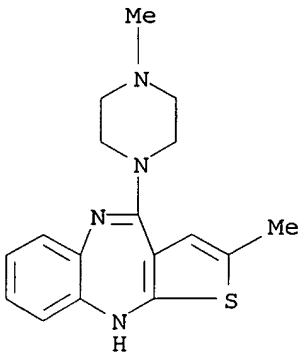
OTHER SOURCE(S): MARPAT 116:83703

AB Title compd. (I) useful for treatment of a disorder of the central nervous system (no data) was prepd. 4-Amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine-HCl (prepn. given) was refluxed in N-methylpiperazine, DMSO and MePh, under N atm. for 20 h to give I. Pharmaceutical formulations contg. I are given.

IT **132539-06-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as nervous system agent)

RN 132539-06-1 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 34 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1988:563459 CAPLUS

DOCUMENT NUMBER: 109:163459

TITLE: Dopamine neurochemical profile of atypical antipsychotics resembles that of D-1 antagonists

AUTHOR(S): Altar, C. A.; Boyar, W. C.; Wasley, A.; Gerhardt, S. C.; Liebman, J. M.; Wood, P. L.

CORPORATE SOURCE: Pharm. Div., Ciba-Geigy Corp., Summit, NJ, 07901, USA

SOURCE: Naunyn-Schmiedeberg's Arch. Pharmacol. (1988), 338(2), 162-8
CODEN: NSAPCC; ISSN: 0028-1298

DOCUMENT TYPE: Journal

LANGUAGE: English

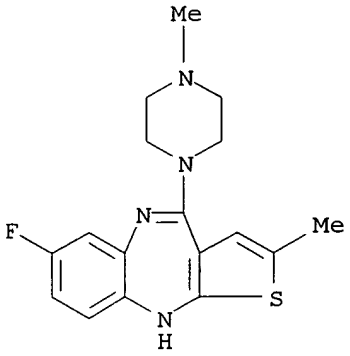
AB The release and metab. of dopamine in the mouse caudate-putamen were detd. after the oral administration of antipsychotic drugs at doses equal to or 6-fold greater than the ED50 dose for their inhibition of apomorphine-induced climbing. Dopamine release was equated with concns. of 3-methoxytyramine (3-MT) and metab. was equated with concns. of dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) levels. Like the D-1 antagonists SCH 23390 and SKF 83566,

most antipsychotic agents with an atypical preclin. profile suggestive of low extrapyramidal symptomatol. (CGS 10746B, flumezapine, CL 77328, rimcazole, clozapine, RM1 81582, and fluperlapine) never increased dopamine release and **produced** variable increases in dopamine metab. Other atypical antipsychotics (thioridazine, mesoridazine, melperone) increased dopamine release at only one dose tested but increased dopamine metab. at most doses. Antipsychotic agents assocd. with extrapyramidal side effects (setoperone, perlapine, haloperidol, chlorpromazine, and metoclopramide) increased dopamine release and metab. at almost every dose tested. Thus, atypical antipsychotics increase the metab. but not release of dopamine at behaviorally EDs. The resemblance of these minimal effects on dopamine release to those obtained with D-1 antagonists that also have an atypical preclin. profile suggests that a mechanism related to D-1 receptor antagonism may contribute to the action of atypical antipsychotics.

IT **61325-80-2**, Flumezapine
RL: BIOL (Biological study)
(dopamine release and metab. in caudate-putamen response to, D-1 receptor antagonism in relation to)

RN 61325-80-2 CAPLUS

CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-fluoro-2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




L5 ANSWER 35 OF 35 CAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1980:560947 CAPLUS

DOCUMENT NUMBER: 93:160947

TITLE: Heteroarenobenzodiazepines. 3. 4-Piperazinyl-10H-thieno[2,3-b][1,5]benzodiazepines as potential neuroleptics

AUTHOR(S): Chakrabarti, Jiban K.; Horsman, Linda; Hotten, Terrence M.; Pullar, Ian A.; Tupper, David E.; Wright, Francesca C.

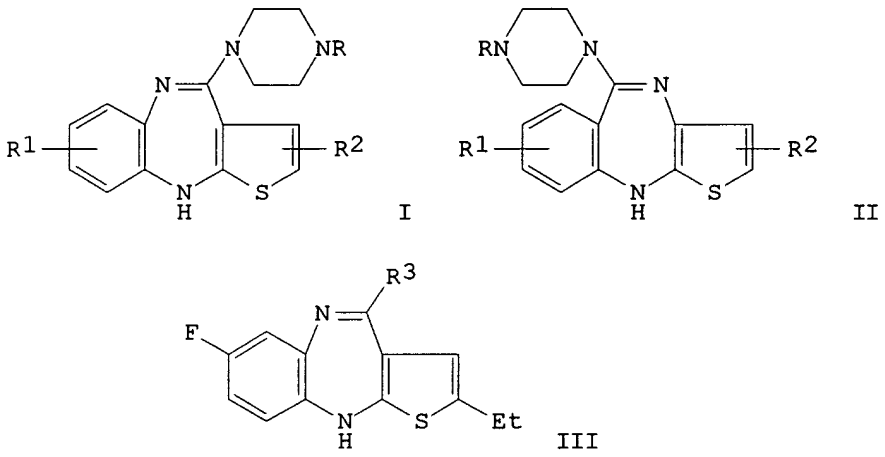
CORPORATE SOURCE: Lilly Res. Cent. Ltd., Windlesham/Surrey, GU20 6PH, Engl.

SOURCE: J. Med. Chem. (1980), 23(8), 878-84
CODEN: JMCMAR; ISSN: 0022-2623

DOCUMENT TYPE: Journal

LANGUAGE: English

GI

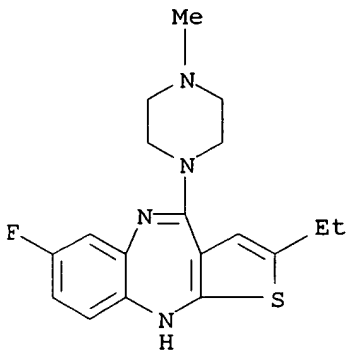


AB The **synthesis** of 59 title compds. I, II, and III (R = H, Me, CO2Ph, etc.; R1 = H, R, Cl, SO2Me, etc.; R2 = H, alkyl, Ph, Ac, etc.; R3 = NHCH2CH2OH, morpholino, piperidino, etc.) is described. The compds. were tested for their activity to block conditional avoidance responses and to **produce** catalepsy in rats. Several I had potent neuroleptic activity and maintained a favorable sepn. of the tested activities. The benzodiazepines II, analogous to I, were inactive. Structure activity relations are discussed.

IT **61325-70-0P 61325-72-2P 61325-74-4P**
**61325-76-6P 61325-77-7P 61325-78-8P**
**61325-80-2P 61325-87-9P 61325-89-1P**
**61325-90-4P 61325-99-3P 61326-00-9P**
**61326-01-0P 61326-06-5P 61326-08-7P**
**61326-14-5P 61326-15-6P 61326-34-9P**
**61326-36-1P 61326-37-2P 61354-11-8P**
**61431-29-6P 61431-30-9P 74162-33-7P**
**74162-34-8P 74162-35-9P 74162-36-0P**
**74162-37-1P 74162-38-2P 74162-39-3P**
**74162-40-6P 74162-41-7P 74162-42-8P**
**74162-43-9P 74162-44-0P 74162-45-1P**
**74162-46-2P 74162-47-3P 74162-49-5P**
**74162-50-8P 74162-51-9P 74162-52-0P**
**74162-53-1P 74162-54-2P 74162-69-9DP,**
derivs.
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and neuroleptic activity of, structure in relation to)

RN 61325-70-0 CAPLUS

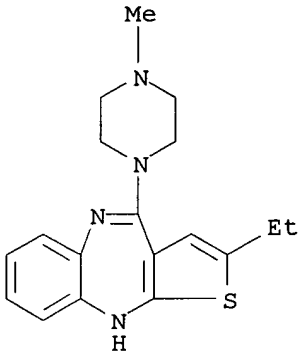
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-7-fluoro-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



RN 61325-72-2 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-4-(4-methyl-1-piperazinyl)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

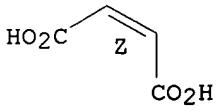
CRN 61325-71-1
CMF C18 H22 N4 S



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

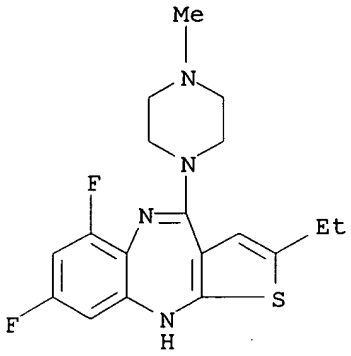
Double bond geometry as shown.



RN 61325-74-4 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-6,8-difluoro-4-(4-methyl-1-piperazinyl)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

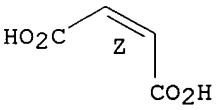
CRN 61325-73-3
CMF C18 H20 F2 N4 S




CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

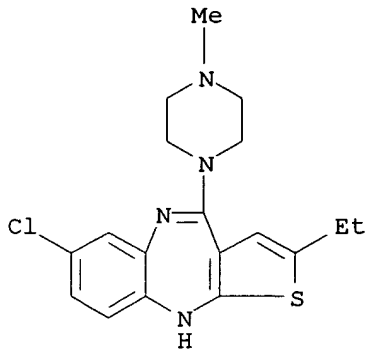
Double bond geometry as shown.




RN 61325-76-6 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-chloro-2-ethyl-4-(4-methyl-1-piperazinyl)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

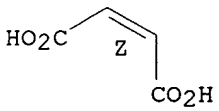
CRN 61325-75-5
CMF C18 H21 Cl N4 S



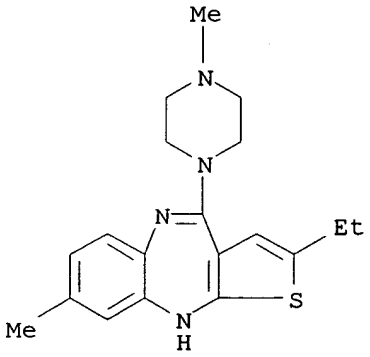
CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

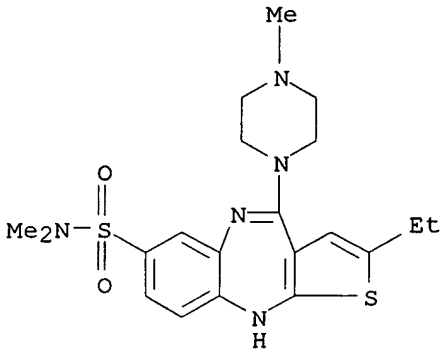
Double bond geometry as shown.



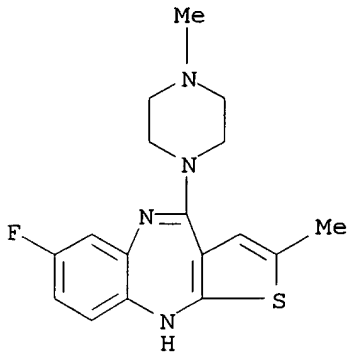
RN 61325-77-7 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-8-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



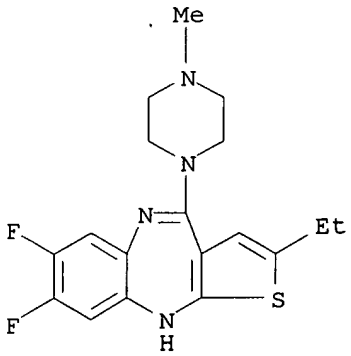
RN 61325-78-8 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine-7-sulfonamide, 2-ethyl-N,N-dimethyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



RN 61325-80-2 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-fluoro-2-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



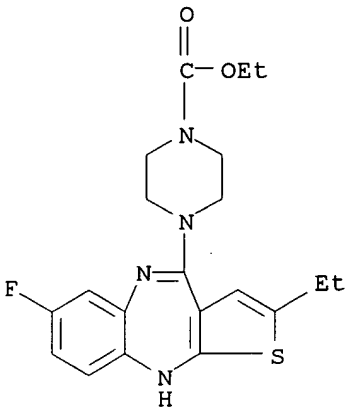
RN 61325-87-9 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-7,8-difluoro-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



RN 61325-89-1 CAPLUS
CN 1-Piperazinecarboxylic acid, 4-(2-ethyl-7-fluoro-10H-thieno[2,3-b][1,5]benzodiazepin-4-yl)-, ethyl ester, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

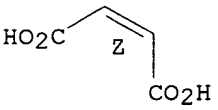
CRN 61325-88-0
CMF C20 H23 F N4 O2 S



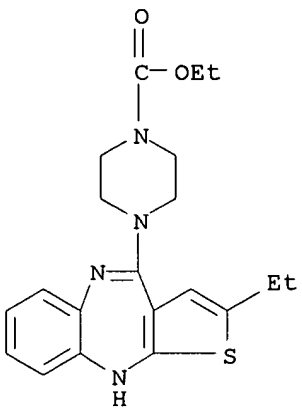
CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

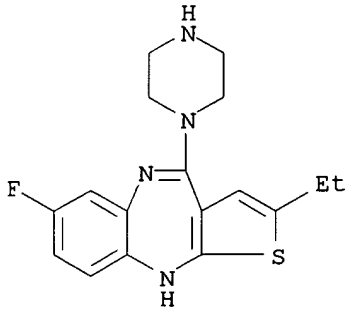
Double bond geometry as shown.



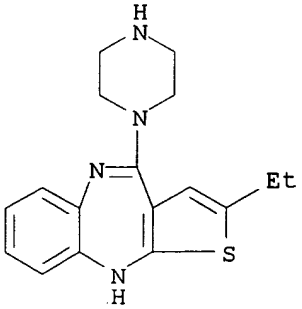
RN 61325-90-4 CAPLUS
CN 1-Piperazinecarboxylic acid, 4-(2-ethyl-10H-thieno[2,3-b][1,5]benzodiazepin-4-yl)-, ethyl ester (9CI) (CA INDEX NAME)



RN 61325-99-3 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-7-fluoro-4-(1-piperazinyl)- (9CI) (CA INDEX NAME)

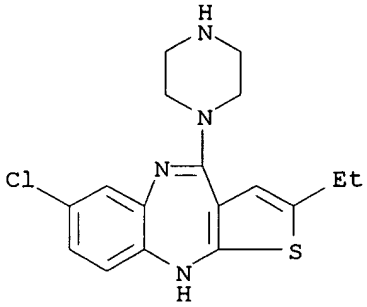


RN 61326-00-9 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-4-(1-piperazinyl)- (9CI) (CA INDEX NAME)

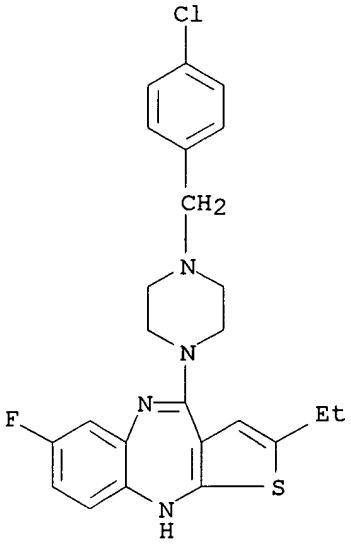


RN 61326-01-0 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-chloro-2-ethyl-4-(1-

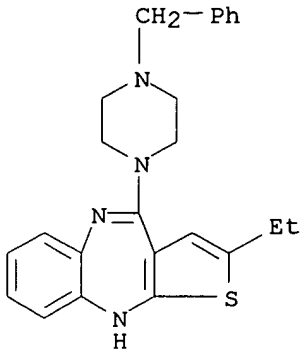
piperazinyl)- (9CI) (CA INDEX NAME)



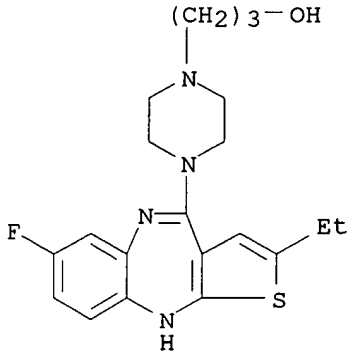
RN 61326-06-5 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 4-[4-[(4-chlorophenyl)methyl]-1-piperazinyl]-2-ethyl-7-fluoro- (9CI) (CA INDEX NAME)



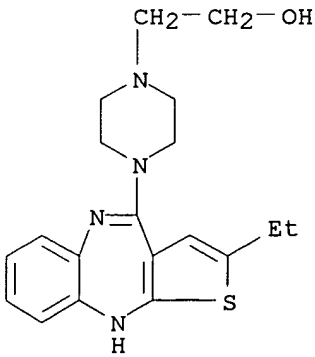
RN 61326-08-7 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-4-[4-(phenylmethyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)



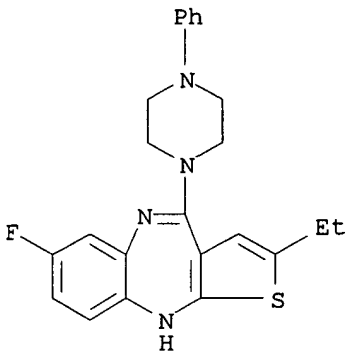
RN 61326-14-5 CAPLUS
CN 1-Piperazinepropanol, 4-(2-ethyl-7-fluoro-10H-thieno[2,3-b][1,5]benzodiazepin-4-yl)- (9CI) (CA INDEX NAME)



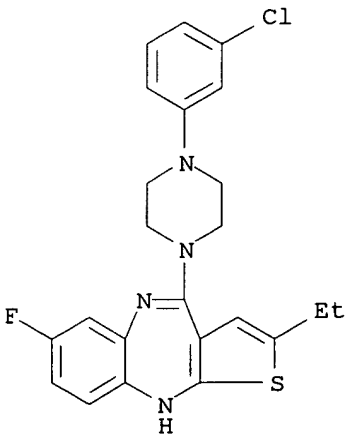
RN 61326-15-6 CAPLUS
CN 1-Piperazineethanol, 4-(2-ethyl-10H-thieno[2,3-b][1,5]benzodiazepin-4-yl)- (9CI) (CA INDEX NAME)



RN 61326-34-9 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-7-fluoro-4-(4-phenyl-1-piperazinyl)- (9CI) (CA INDEX NAME)

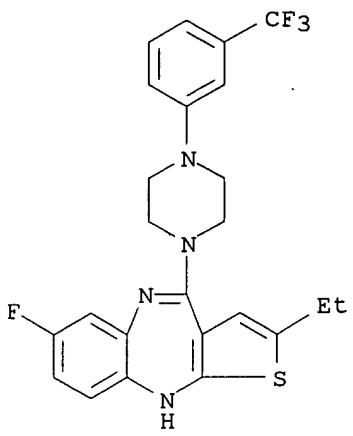



RN 61326-36-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 4-[4-(3-chlorophenyl)-1-piperazinyl]-2-ethyl-7-fluoro-, monohydrochloride (9CI) (CA INDEX NAME)



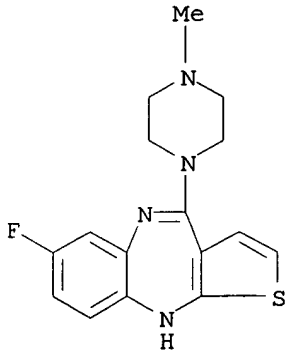

● HCl

RN 61326-37-2 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-7-fluoro-4-[4-[3-(trifluoromethyl)phenyl]-1-piperazinyl]-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

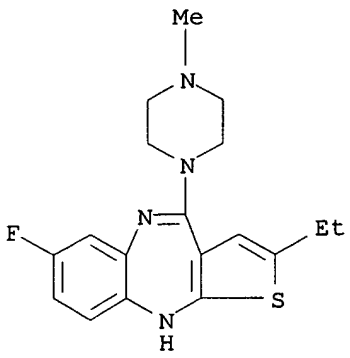
RN 61354-11-8 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-fluoro-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



RN 61431-29-6 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-7-fluoro-4-(4-methyl-1-piperazinyl)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

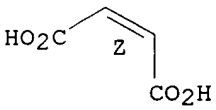
CRN 61325-70-0
CMF C18 H21 F N4 S



CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

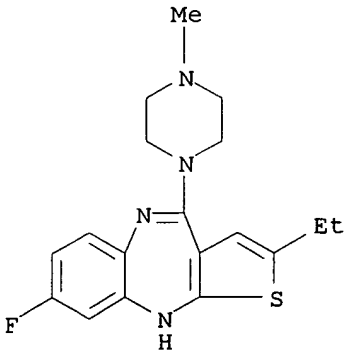
Double bond geometry as shown.



RN 61431-30-9 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-8-fluoro-4-(4-methyl-1-piperazinyl)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

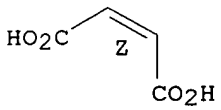
CRN 61325-69-7
CMF C18 H21 F N4 S



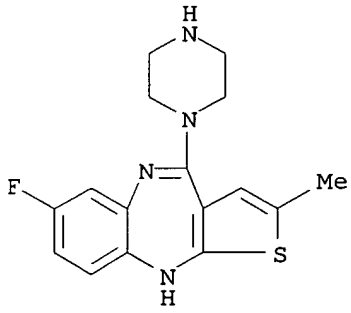
CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.



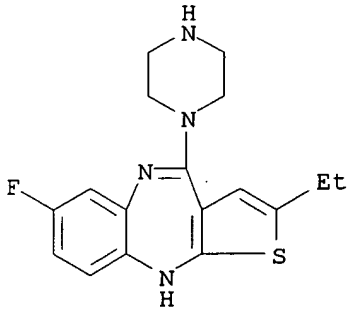
RN 74162-33-7 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-fluoro-2-methyl-4-(1-piperazinyl)- (9CI) (CA INDEX NAME)



RN 74162-34-8 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-7-fluoro-4-(1-piperazinyl)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

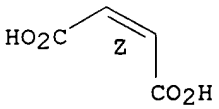
CRN 61325-99-3
CMF C17 H19 F N4 S



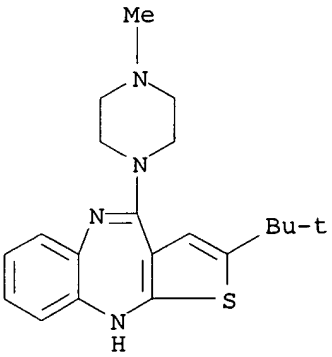
CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

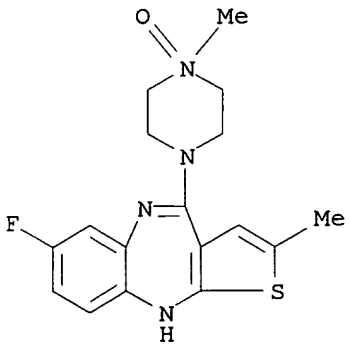
Double bond geometry as shown.



RN 74162-35-9 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-(1,1-dimethylethyl)-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)

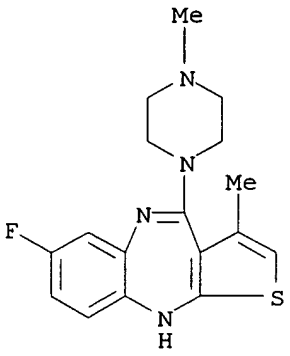


RN 74162-36-0 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-fluoro-2-methyl-4-(4-methyl-4-oxido-1-piperazinyl)- (9CI) (CA INDEX NAME)

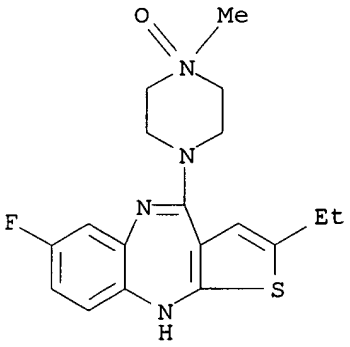


RN 74162-37-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-fluoro-3-methyl-4-(4-methyl-

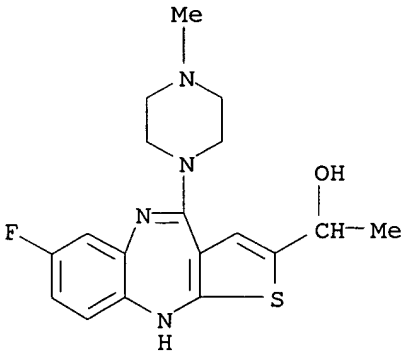
1-piperazinyl)- (9CI) (CA INDEX NAME)



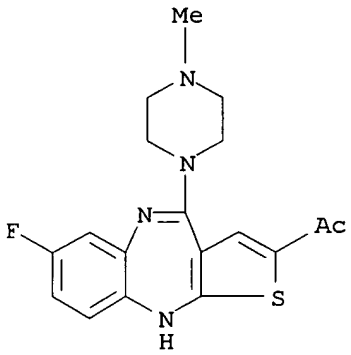
RN 74162-38-2 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-7-fluoro-4-(4-methyl-4-oxido-1-piperazinyl)- (9CI) (CA INDEX NAME)



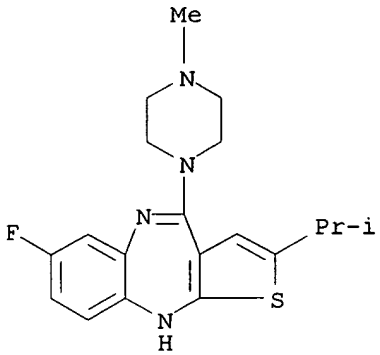
RN 74162-39-3 CAPLUS
CN 2H-Thieno[2,3-b][1,5]benzodiazepine-2-methanol, 7-fluoro-.alpha.-methyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



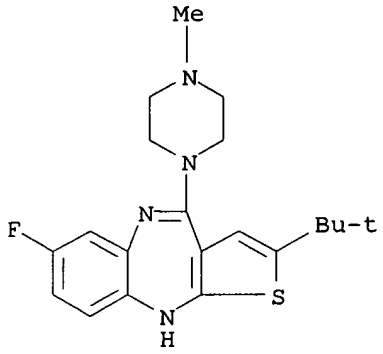
RN 74162-40-6 CAPLUS
CN Ethanone, 1-[7-fluoro-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepin-2-yl]- (9CI) (CA INDEX NAME)



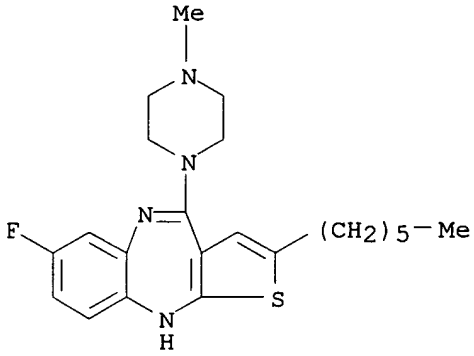

RN 74162-41-7 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-fluoro-2-(1-methylethyl)-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



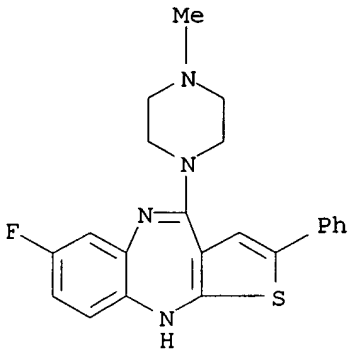

RN 74162-42-8 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-(1,1-dimethylethyl)-7-fluoro-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



RN 74162-43-9 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-fluoro-2-hexyl-4-(4-methyl-1-piperazinyl)- (9CI) (CA INDEX NAME)

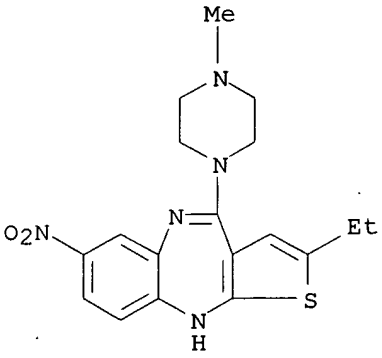


RN 74162-44-0 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 7-fluoro-4-(4-methyl-1-piperazinyl)-2-phenyl-, dihydrochloride (9CI) (CA INDEX NAME)

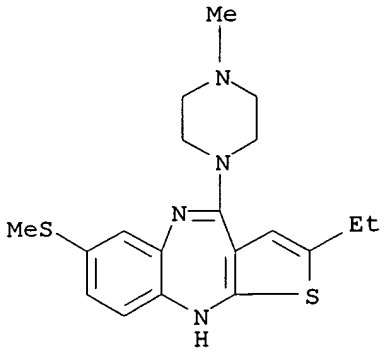


● 2 HCl

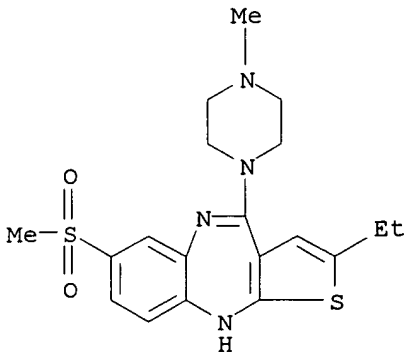
RN 74162-45-1 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-4-(4-methyl-1-piperazinyl)-7-nitro- (9CI) (CA INDEX NAME)



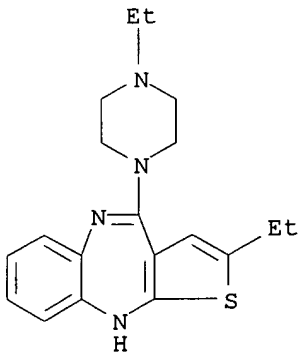
RN 74162-46-2 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-4-(4-methyl-1-piperazinyl)-7-(methylthio)- (9CI) (CA INDEX NAME)



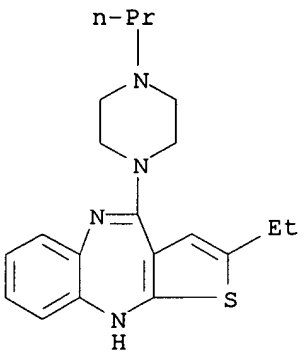
RN 74162-47-3 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-4-(4-methyl-1-piperazinyl)-7-(methylsulfonyl)- (9CI) (CA INDEX NAME)



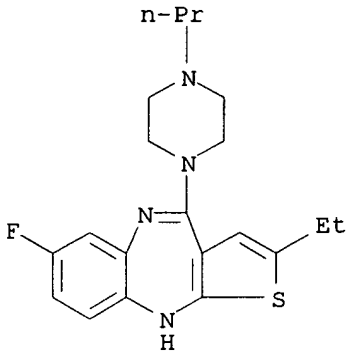
RN 74162-49-5 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-4-(4-ethyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



RN 74162-50-8 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-4-(4-propyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



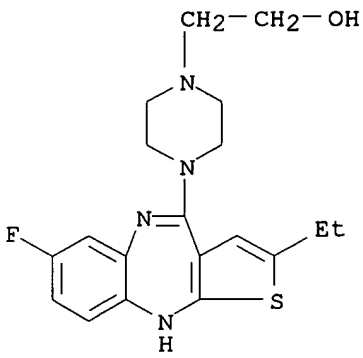

RN 74162-51-9 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-7-fluoro-4-(4-propyl-1-piperazinyl)- (9CI) (CA INDEX NAME)




RN 74162-52-0 CAPLUS
CN 1-Piperazineethanol, 4-(2-ethyl-7-fluoro-10H-thieno[2,3-b][1,5]benzodiazepin-4-yl)-, (2Z)-2-butenedioate (1:2) (salt) (9CI) (CA INDEX NAME)

CM 1

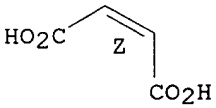
CRN 61326-12-3
CMF C19 H23 F N4 O S



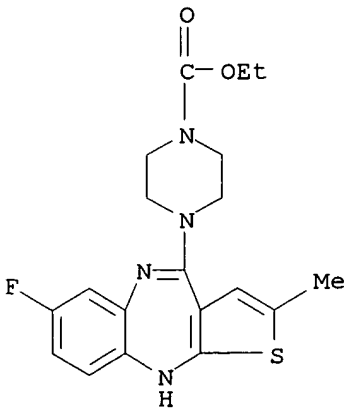
CM 2

CRN 110-16-7
CMF C4 H4 O4
CDES 2:Z

Double bond geometry as shown.

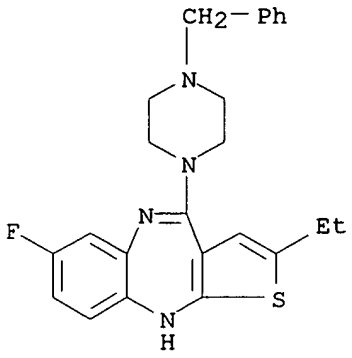


RN 74162-53-1 CAPLUS
CN 1-Piperazinecarboxylic acid, 4-(7-fluoro-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepin-4-yl)-, ethyl ester (9CI) (CA INDEX NAME)



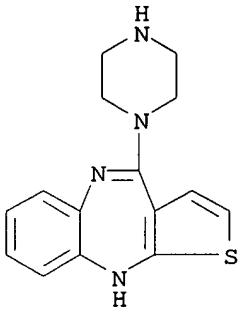
RN 74162-54-2 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 2-ethyl-7-fluoro-4-[4-(phenylmethyl)-1-piperazinyl]-, dihydrochloride (9CI) (CA INDEX

NAME)



● 2 HCl

RN 74162-69-9 CAPLUS
CN 10H-Thieno[2,3-b][1,5]benzodiazepine, 4-(1-piperazinyl)- (9CI) (CA INDEX NAME)



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(FILE 'HOME' ENTERED AT 10:45:31 ON 11 JAN 1999)

FILE 'REGISTRY' ENTERED AT 10:45:37 ON 11 JAN 1999
L1 STRUCTURE UPLOADED
L2 5 S L1
L3 104 S L1 FUL

FILE 'CAPLUS' ENTERED AT 10:46:09 ON 11 JAN 1999
L4 182 S L3
L5 35 S L4 AND (PREPARAR? OR PREPARATION OR PRODUC? OR SYNTHESI

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 138.31 | 258.76 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -18.74 | -18.74 |

STN INTERNATIONAL LOGOFF AT 10:49:35 ON 11 JAN 1999